CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212854Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research| Office of Surveillance and Epidemiology (OSE)

Epidemiology: Sufficiency Memo for Using ARIA to Evaluate the Risk of Needlestick injury Associated with ZIMHI™ use

Date:	September 29, 2021
Acting Team Leader:	Mingfeng Zhang, M.D., Ph.D. Division of Epidemiology II
Deputy Division Director:	Monique Falconer, M.D., M.S. Division of Epidemiology II
OPE Director:	Judith Zander, M.D.
FDA Sentinel Program Lead:	Sarah Dutcher, PhD (designee)
OSE Deputy Director:	Robert Ball MD, MPH, ScM
Subject:	Sufficiency Memo for Using ARIA to Evaluate the Risk of Needlestick injury Associated with ZIMHI™ use
Drug Name(s):	Naloxone HCl injection (ZIMHI™)
Application Type/Number:	NDA 212854
Applicant/sponsor:	Adamis Pharmaceuticals Corporation
OSE RCM #:	2021-1256

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	X

1. BACKGROUND INFORMATION

1.1. Medical Product

ZIMHI is a drug-device combination product designed to deliver 5 mg of naloxone in 0.5 mL in a single use pre-filled syringe. It is intended for intramuscular (IM) or subcutaneous (SC) injection at the anterolateral thigh. The indication sought for ZIMHI is emergency treatment for known or suspected opioid overdose in the community setting by untrained personnel.

Adamis, the applicant, submitted a New Drug Application (NDA 212854) under 505(b)(2), which is under review by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP).

1.2. Describe the Safety Concern

The medical device for ZIMHI is designed with a manually activated needle safety guard to cover the exposed needle after the injection. Although no needlestick injuries have been reported for the approved epinephrine product SYMJEPI which uses the same device as ZIMHI, the applicant has not provided data to demonstrate the success rate of deployment of the needle guard among laypersons without training using the device.

ZIMHI is expected to be widely used in community settings in a patient population with an increased rate of bloodborne pathogens disease than the general public. And it is expected that it will be administered by untrained personnel unfamiliar with how to administer the product. If this product is approved, DAAP is concerned about potential risks of transmission of bloodborne pathogens such as HIV, Hepatitis B, and Hepatitis C from opioid-overdose patients to untrained personnel administering the injection and bystanders injured by exposed needles after device disposal due to the failure of the deployment of the needle safety guard by the administrators.

This device-related safety concern regarding needle safety was one of the reasons for the Complete Response during the second cycle review for this product. In this resubmission, the applicant proposed additional safety measures, including:

- Additional labeling on the ZIMHI device and outer plastic case to emphasize use of the needle shield
- Educational programs directed at patients and user of the ZIMHI device, including training with a demonstration video and a trainer device upon prescription or dispensation
- A pharmacovigilance program that will seek out reports of accidental needle sticks and consider whether additional safety measures are necessary

DAAP disagrees that the applicant-proposed pharmacovigilance plan can fully address the device-related safety concerns; however, they believe the benefit of this community-use naloxone product outweighs the potential device-related safety concerns. Therefore, DAAP plans to approve this product with a Post-Marketing Requirement (PMR) to evaluate the prevalence of needlestick injuries associated with the use of ZIMHI.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

A post-marketing study to evaluate the risk of needlestick injury to persons administering ZIMHI.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Not Applicable.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The population at risk are the administrators of the ZIMHI and bystanders exposed to the device afterwards.

2.2 Is ARIA sufficient to assess the intended population?

No. Although Sentinel should be able to capture patients who got ZIMHI dispensing, the population at risk for needlestick injury are those who administer ZIMHI and those who are injured by exposed needles after device disposal due to the failure of the deployment of the needle safety guard by the administrators. This population is unlikely to be captured in the system. Therefore, ARIA is insufficient to capture the population at risk for needlestick injury.

3 EXPOSURES

3.1 Treatment Exposure(s)

This study evaluates needlestick injury in the population administering the injection and bystanders injured by exposed needles after device disposal, so there's no drug exposure for them.

3.2 Comparator Exposure(s)

Skipped given the response in Section 3.1.

3.3 Is ARIA sufficient to identify the exposure of interest?

Not Applicable.

4 OUTCOME(S)

4.1 Outcomes of Interest

Any needlestick injuries, including the minor needlestick injuries.

4.2 Is ARIA sufficient to assess the outcome of interest?

No. Although there are ICD codes for needlestick injuries (ICD-10: W46.1XXA for "Contact with contaminated hypodermic needle"; and ICD-9: E920.5 for "Accidents caused by hypodermic needle"), these codes have not been validated. This study intends to capture any needlestick injury, including the minor injuries, so the sensitivity of these codes is a major concern. In addition, given that such an injury likely happens during an opioid rescue emergency, the incident is likely to not be reported or under reported as with needlestick injuries among hospital workers[1]. In addition, review of medical records would be needed to obtain information on cause of needlestick injuries. Therefore, ARIA is insufficient for outcome assessment.

5 COVARIATES

5.1 Covariates of Interest

This study evaluates the crude incidence of needletsick injury, so no covariates are needed.

5.2 Is ARIA sufficient to assess the covariates of interest?

Not Applicable.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

A study to evaluate the prevalence of needlestick injuries associated with the administration of ZIMHI, along with a detailed analysis of incidents, including full event narratives of the incidents and any subsequent adverse events, and root cause analysis for the reported events.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

No. Sentinel does not capture clinical narratives and the accurate timeline of relevant events. Therefore, root cause analysis is not possible in the ARIA system.

7 NEXT STEPS

The Division of Epidemiology II (DEPI) determined that ARIA is insufficient for evaluating the prevalence of needlestick injuries associated with the use of ZIMHI.

We also assessed the feasibility of other epidemiologic data sources. Although we found a database (the NEMSIS database) that collects information on work-related needlestick injury for emergency medical service (EMS) crew members, it is unclear how these incidents can be linked to naloxone injection or the completeness of reporting of these incidents. Also, NEMSIS would not capture all at-risk populations, such as non-medical professionals who might have to administer this product in an emergency or inadvertently come into contact with a device in which the safety had not been deployed (e.g., family members, bystanders). So, we cannot generalize the risk of needlestick injury among trained EMS crew members to all end users of this product.

Considering the broad and unpredictable population at risk, DEPI concluded that it would be challenging to design and conduct a post-marketing study to evaluate the incidence of needlestick injury related to the administration of ZIMHI using either a registry study or a database study.

DAAP plans to issue a PMR in which the applicant will need to propose a study to address the Agency's concern of needlestick injuries associated with the administration of ZIMHI. The draft PMR language is below.

> *PMR #2: Conduct a study on the prevalence of needlestick injuries associated with the use of ZIMHI. Provide a detailed analysis of incidents (including reported incidents that did, as well as did not, result in patient and/or provider harm), full event narratives of the incidents and any subsequent adverse events, and the results of root cause analysis performed for the reported event.*

Reference:

1. Bahat H, Hasidov-Gafni A, Youngster I, Goldman M, Levtzion-Korach O. The prevalence and underreporting of needlestick injuries among hospital workers: a cross-sectional study. *Int J Qual Health Care.* 2021;33(1).

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 29, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 212854
Product Name and Strength:	Zimhi (naloxone hydrochloride) injection, 5 mg/0.5 mL
Applicant/Sponsor Name:	Adamis Pharmaceuticals Corporation
OSE RCM #:	20219-8-3
DMEPA 1 Safety Evaluator:	Cameron Clark, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised labels and labeling received via email to Jungwon Chin on September 10, 2021, September 20, 2021 and September 29, 2021 for Zimhi. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised labels and labeling for Zimhi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

In our previous review[a] we requested that Adamis add the route of administration (ROA) to the principal display panel (PDP) of the syringe label. In their response, Adamis stated that they are unable to accommodate this request as there is lack of space to add the ROA and there is more critical information included on the PDP. They also noted that the ROA is included on the case labeling. Due to the lack of space on the PDP of the syringe label, we find it acceptable that it is omitted given that it is already including on the case labeling.

[a] Clark, C. Label and Labeling Review for Zimhi (NDA 212854). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 AUG 26. RCM No.: 2019-8-2.

Reference ID: 4865063

Additionally, in our previous review[a] we requested that Adamis add the statement, "After Use call 911" to the PDP of the syringe label. In their September 10, 2021 response to our recommendations, Adamis added the statement "After Use call 911" directly below the statement "Insert Needle in Thigh". We were concerned that the placement of the "After Use call 911" statement may result in users overlooking the "push plunger" and/or "slide (b) (4) safety guard" statements which could result in dose omission or needlestick injuries. Therefore, on September 16, 2021 we sent an Information Request (IR)[b] to Adamis and recommended that the "After Use call 911" statement be removed from the PDP of the syringe label and instead added as a 5th step on the PDP of the case labeling. We also requested that they ensure that images of the syringe label and case labeling are revised in all other labeling (i.e. pull-out IFU, IFU located within the PI, all training materials) to be consistent with this revision. In their September 20, 2021 response, Adamis submitted revised labels and labeling to incorporate our recommendation.

Furthermore, in our previous review[a] we requested that Adamis label each part of the prefilled syringe , in the PI, IFU located in the PI and the pull-out IFU. In their September 20, 2021 response, in addition to labeling each part of the prefilled syringe, Adamis also (b) (4)

(b) (4)

We also noted that there were several inconsistencies between the IFU in the PI and the pull-out IFU and requested that Adamis ensure that the pull-out IFU is consistent with all revisions made in the IFU in the PI. In their September 29, 2021 submission via email to OND Project Manager Jungwon Chin, Adamis (b) (4) updated both IFU's so that they were consistent with one another.

[b] Chin, J. FDA Communication: NDA 212854 (Zimhi) Information requested 9.16.2021 – Response requested by COB September 20, 2021. Silver Spring (MD): FDA, CDER, DAAP (US); 2021 SEP 16. NDA 212854.

3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 22, 2021

To: Jennifer Nadel, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Jungwon Chin, Regulatory Project Manager, DAAP

Lisa Basham, Associate Director for Labeling, DAAP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZIMHI™ (naloxone hydrochloride) injection for intramuscular or subcutaneous use

NDA: NDA 212854

In response to DAAP's consult request dated June 2, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI)/Instructions for Use (IFU) and carton and container labeling for the original NDA/BLA submission for ZIMHI™ (naloxone hydrochloride) injection for intramuscular or subcutaneous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on September 15, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI/IFU were sent under separate cover on September 22, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 10, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 22, 2021
To:	Joyce Chin, PharmD Regulatory Project Manager **Division of Anesthesiology, Addiction, Medicine, and Pain Medicine (DAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** L. Sheneé Toombs, PharmD, CPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ZIMHI (naloxone hydrochloride)
Dosage Form and Route:	injection, for intramuscular or subcutaneous use
Application Type/Number, Supplement Number:	NDA 212854
Applicant:	Adamis Pharmaceuticals Corporation

1 INTRODUCTION

On May 13, 2021, Adamis Pharmaceuticals Corporation submitted for the Agency's review a resubmission of their New Drug Application (NDA) 212854 for ZIMHI (naloxone hydrochloride) injection. This resubmission provides responses to the Agency's comments from the November 13, 2020 Complete Response (CR) letter. The proposed indication is for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction, Medicine, and Pain Medicine (DAAP) on June 2, 2021 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU)] for ZIMHI (naloxone hydrochloride) injection.

2 MATERIAL REVIEWED

- Draft ZIMHI (naloxone hydrochloride) injection PPI and IFU received on May 13, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 15, 2021.
- Draft ZIMHI (naloxone hydrochloride) injection Prescribing Information (PI) received on May 13, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 15, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memorandum

Date:	September 17, 2021
Reviewer:	Mallika Mundkur, MD MPH, Lead Physician Division of Pharmacovigilance II (DPV II)
Deputy Division Director:	Ida-Lina Diak, PharmD, MS DPV II
Product Name:	Zimhi (Naloxone Hydrochloride)
Subject:	Needlestick Injury
Application Type/Number:	Class 2 Resubmission/NDA 212854
Submission Number:	0063
Applicant:	Adamis Pharmaceuticals Corporation
OSE RCM #:	2021-1116

Reference ID: 4858958

1 INTRODUCTION

In this memorandum, the Division of Pharmacovigilance II (DPV II) comments upon the Risk Management Plan (RMP) submitted with the current application for ZIMHI™ (NDA 212854). DPV II completed this assessment in response to a consult received from the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on June 2, 2021, in which we were asked to review sections pertaining to postmarket surveillance.

ZIMHI™ is a pre-filled syringe of naloxone hydrochloride (5 mg/0.5 mL) intended to be administered intramuscularly (IM) for the emergency treatment of known or suspected opioid overdose. ZIMHI™ uses a manually-deployed need shield which covers the needle and includes a hard case for the device following use (See Appendix A). ZIMHI™ uses the same delivery device for a combination product (SYMJEPI™; NDA 207534) approved and marketed for the treatment of acute allergic reactions by users and caregivers, a product also manufactured by Adamis Pharmaceuticals (henceforth referred to as "the Applicant").

The original application for this product was filed on December 31, 2018 and the current application represents the second resubmission. Following the previous review cycle in 2020, a Complete Response (CR) letter was issued on November 13, 2020, citing several concerns including but not limited to the need for manual deployment of a protective needle shield. An application was re-submitted on May 31, 2021. For the current review cycle, a separate review has been completed by the Division of Medication Error Prevention and Analysis (DMEPA) regarding device design and safety; in that review, the authors concluded "we find that the benefit of having an injectable naloxone hydrochloride prefilled syringe product outweighs the residual risk associated with the user interface design," risk that they felt was not fully mitigated by the Applicant's proposed training program and other changes [a]

2 METHODS

DPV reviewed the RMP in its entirety, although, per DAAP's request, focused primarily on the following: "Comprehensive Safety Surveillance and Reporting Program" (Section 1.16.1.3.2.4).

3 RESULTS

In the RMP, the Applicant proposes several changes they suggest would mitigate the potential risk of needlestick injury, such as including additional labeling on the device and device case, an educational program to train users on proper use of the device and inclusion of a trainer device that could be used for practice prior to actual use. The training video would also instruct users to "seek immediate medical attention if there is an accidental needlestick" and "describe the risk of contracting blood-borne pathogens when administering injectable naloxone." The device itself has not been modified since the previous review cycle in 2020 and no new human factors studies have been conducted for ZIMHI™.

[a] Johnson, C. Label and Labeling Review Memo for Zimhi (naloxone hydrochloride) NDA 212854. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 AUG 26. RCM No.: 2019-8-2.

Reference ID: 4858958

The Applicant cross-references a human factors study conducted for SYMJEPI™ and postmarketing data for that product, concluding that the results from the human factors study (no needlestick injuries) and lack of needlestick injury reported in postmarket reporting databases[b] for SYMJEPI™ indicate that risk of needlestick injury would remain low with ZIMHI™. The Applicant suggests that the main benefits of this product would be higher dose, intramuscular route, and better safety features from the standpoint of needlestick injury than unapproved injectable naloxone that is currently available through so-called "take-home kits."

The Applicant's surveillance plan includes use of a "pharmacovigilance service provider" (not further specified) that will be responsible for various activities: 1) to collect, manage and follow-up on reports submitted to the company relating to adverse events such as needlestick injury or blood-borne infections 2) monitor the published literature 3) perform "data-mining" of the FDA Adverse Event Reporting System (FAERS) to monitor for the risk of needlestick injury (see Appendix B for information on FAERS).

The Applicant (via the service provider) intends to submit both 5-day and 15-day reports, as well as quarterly reports for the first three years, in compliance with pertinent regulations for the product (e.g., 21 C.F.R. § 314.80[c], 21 C.F.R. § 4.102 (d)[d]); the events of needlestick injury and downstream events (e.g., blood-borne infection) will be categorized as "serious" events and included in expedited reporting.

Figure 1. Schematic of Applicant's Proposed Safety Surveillance and Reporting Program*

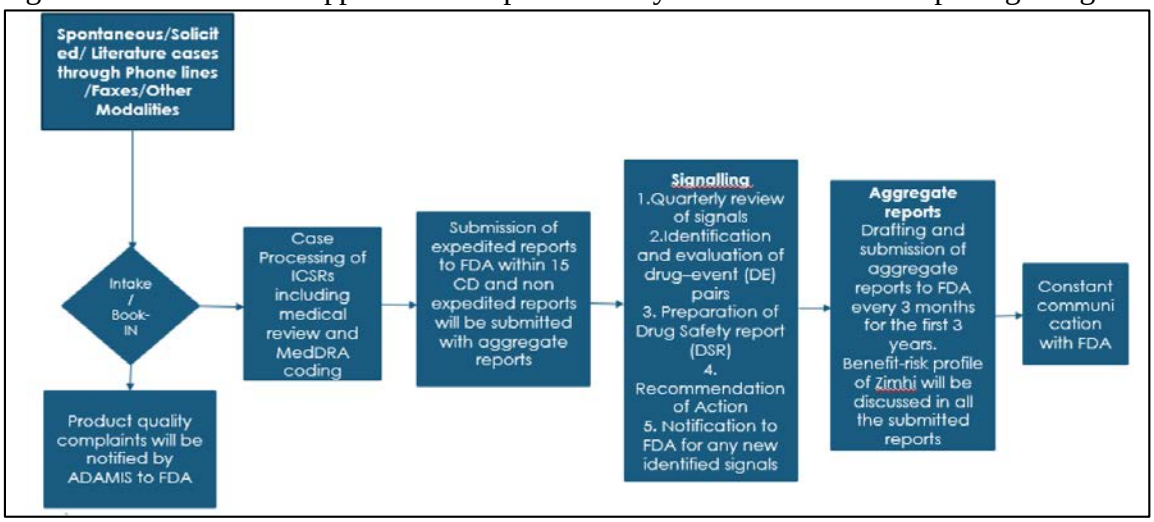

*Figure 12 from Applicant RMP

[b] DPV II conducted an independent search of the FDA Adverse Event Reporting System (FAERS) on September 9, 2021 for reports of needlestick injury with the suspect product Symjepi/NDA 207534 (High Level Group Term- Injuries NEC; Procedural related injuries and complications NEC and Lower Level Term- Accidental needle stick) and did not retrieve any reports using this search strategy.

[c] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.80

[d] https://www.govinfo.gov/content/pkg/CFR-2019-title21-vol1/xml/CFR-2019-title21-vol1-part4.xml#seqnum4.102

Reference ID: 4858958

4 DISCUSSION

The surveillance plan described by the Applicant appears compliant with FDA regulations and reasonable from a pharmacovigilance perspective. By including reports of needlestick injury and blood-borne infection with expedited reports, the Applicant appears committed to monitoring these events more closely, regardless of whether or not they are described in labeling. That said, a surveillance plan relying exclusively on spontaneous reports to monitor events occurring in the community will almost certainly under-capture events of interest such as needlestick injury. The enhanced training programs offered by the Applicant may to some extent reduce the likelihood of needlestick injury. However, such training will not reduce the risk of such injury among untrained users.

We note the challenges of collecting data on needlestick injury in the context of community use by untrained laypersons, and postmarket surveillance of this potential issue will likely be limited. As such, at this time, we do not have specific suggestions regarding improvements to the surveillance plan proposed by the Applicant.

Reference ID: 4858958

5 APPENDICES

5.1 APPENDIX A. PRODUCT SAFETY FEATURES

Figure 1. Manually Deployed Needle Shield

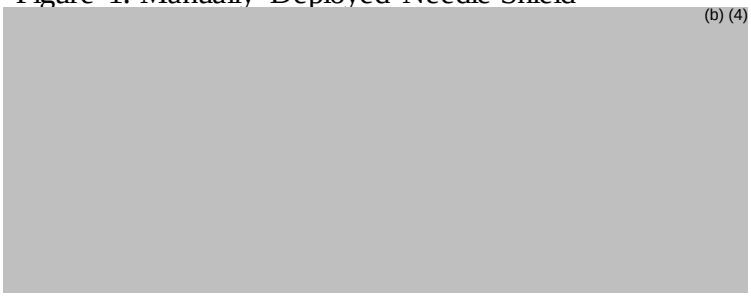

Figure 2. Hard Case for Used Device

5.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a

Reference ID: 4858958

product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 26, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 212854
Product Name and Strength:	Zimhi (naloxone hydrochloride) injection, 5 mg/0.5 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Adamis Pharmaceuticals Corporation
FDA Received Date:	5/13/2021, 6/2/2021 and 8/13/2021
OSE RCM #:	2019-8-2
DMEPA 1 Safety Evaluator:	Cameron Clark, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Division Director (Acting):	Irene Z. Chan, PharmD, BCPS

Reference ID: 4847903

1 REASON FOR REVIEW

As part of the approval process for Zimhi (naloxone hydrochloride) injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Zimhi prescribing information, instructions for use, container labels and carton labeling for areas of vulnerability that may lead to medication errors. We were also requested to evaluate Adamis's risk mitigation strategies (i.e. training materials, pharmacovigilance plan) that are proposed to reduce the risk of needlestick injuries.

1.1 REGULATORY HISTORY

Adamis originally submitted NDA 212854 on December 31, 2018. To justify not submitting the results of a human factors (HF) validation study, Adamis provided a use-related risk analysis (URRA) and comparative analyses (CA) which compared the proposed Zimhi (naloxone hydrochloride) injection to Adamis's currently approved Symjepi (epinephrine hydrochloride) injection, NDA 207534. We reviewed the URRA and CA and found that there were no differences between the Symjepi and Zimhi user interfaces that impacted critical tasks.[a] We agreed with Adamis's justification for not submitting the results of an HF validation study for Zimhi. During the review cycle, we also reviewed the IFU, container labels, and carton labeling from a medication error perspective and our recommendations[b] were conveyed to Adamis. However, a Complete Response (CR) letter was issued to Adamis on November 22, 2019 due to product quality, nonclinical, clinical pharmacology, and CDRH-related device deficiencies.[c]

Adamis submitted their complete response to the clinical and CDRH-related device deficiencies on May 15, 2020 as a class 2 resubmission. We reviewed the IFU, container labels and carton labeling and provided additional recommendations from a medication error perspective.[d] During the second review cycle, DAAP clinical expressed concerns about the risk of accidental needlestick injuries and transmission of blood borne pathogens from the opioid overdose patient to the user (person who would administer Zimhi). Because of the identified differences in transmission of blood borne pathogens between patients for Symjepi and patients for Zimhi, DAAP clinical expressed concern that by leveraging from Symjepi, Adamis did not provide adequate data to demonstrate that intended users are able to safely deploy the needle safety guard without difficulties. While DMEPA did not disagree that the design of the needle safety guard could be further optimized to minimize the risk for needlestick injury, we determined

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[a] Flint, J. URRA, CA, and Label and Labeling Review for Zimhi (naloxone hydrochloride) NDA 212854. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 24. RCM No.: 2019-8 and 2019-15.

[b] Flint, J. URRA, CA, and Label and Labeling Review for Zimhi (naloxone hydrochloride) NDA 212854. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 24. RCM No.: 2019-8 and 2019-15.

[c] Patwardhan, S. Complete Response Letter for Zimhi. Silver Spring (MD): FDA, CDER, DAAP (US); 2019 NOV 11. NDA 212854.

[d] Johnson, C. Label and Labeling Review Memo for Zimhi (naloxone hydrochloride) NDA 212854. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 04. RCM No.: 2019-8-1.

that additional HF data was not necessary and that the residual risk should be found acceptable in light of the public health need for naloxone products. However, DAAP continued to remain concerned, and on November 13, 2020, a second CR letter was issued to NDA 212854 due to clinical and CDRH-related device deficiencies.[e] The clinical deficiency noted that Adamis did not provide adequate data to support safe use. To address the deficiency DAAP Clinical proposed a redesign of the syringe to include an automatically deploying needle safety guard. Because the clinical deficiency requested a redesign of the device-constituent part, we requested that Adamis submit the results of an HF validation study for our review if the user interface was redesigned.

On February 12, 2021, Adamis submitted a Type A meeting request to discuss the CR deficiencies. During the April 8, 2021 teleconference[f], Adamis emphasized the public health need for their naloxone hydrochloride injection given the current opioid crisis. (b) (4) To address the Agency's concerns, Adamis proposed labeling revisions, a training program, and pharmacovigilance plans to mitigate the risk of accidental needlestick injuries with their current design. The Agency stated that due to safety concerns and for the betterment of the device, Adamis should strongly consider redesigning the device. Additionally, the Agency stated that if the application is approved with the current device, Adamis could redesign/improve the device in the future. Furthermore, the Agency advised Adamis to provide the details and specific risk mitigation measures they intend to implement in the NDA resubmission for agency review and evaluation.

Therefore, on May 13, 2021, Adamis submitted their complete response to the clinical and device CR deficiencies as a class 2 resubmission.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other – Information Requests	E

[e] Patwardhan, S. Complete Response Letter for Zimhi. Silver Spring (MD): FDA, CDER, DAAP (US); 2020 NOV 13. NDA 212854.

[f] Patwardhan, S. Meeting Minutes for Zimhi (naloxone hydrochloride). Silver Spring (MD): FDA, CDER, DAAP (US); 2021 MAY 07. NDA 212854.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

In order to address the Agency's concern for the risk of accidental needlestick injuries and potential transmission of blood borne pathogens, Adamis has proposed labeling revisions and an educational program directed at patients and users, including instructional video/slides and a trainer device to "further ensure that users properly use the needle safety shield and case." Additionally, Adamis proposes to implement a pharmacovigilance mitigation strategy[g] designed to aid in detecting accidental needlestick injuries and to determine if additional safety measures are necessary. We provide a summary of each proposal and our assessment below.

3.1 LABELING

During the previous review cycle, Adamis proposed the following syringe label (Figure A) and case labeling (Figure B):

Figure A. Syringe label

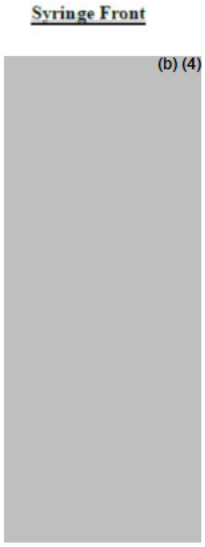
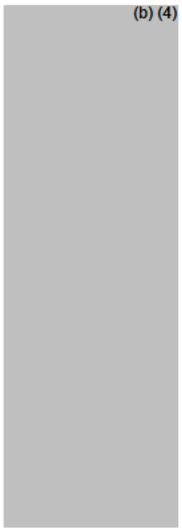


Figure B. Case Labeling



[g] Zimhi Risk Assessment (NDA 212854). San Diego (CA): Adamis Pharmaceuticals Corporation; 2021 MAY 13. Available from: \\CDSESUB1\evsprod\nda212854\0063\m1\us\zimhi-risk-assessment-non-rems.pdf.

(b) (4)

To address the concern for needlestick injuries, Adamis has proposed to include a 4th step, "Slide down safety guard" to the syringe label and case labeling (see Figure C below). Adamis, also added the number "4" within (b) (4) hexagon to the corresponding instruction in the IFU.

Figure C. Revised Syringe label and case labeling

(b) (4)

Adamis indicated that they included this 4th step to alert users that deploying the needle safety guard on the Zimhi device as an important part of the safe and effective use of the product.

During our initial review, we were concerned that the addition of the 4th step to the syringe label and case labeling may lead to unintended consequences such as the user prematurely deploying the needle guard. Therefore, on May 28, 2021, we sent an Information Request (IR) to Adamis, requesting data to support the labeling revisions. In their June 2, 2021 response[h], Adamis noted that they are relying on data from their previous Symjepi HF program. They noted that while the 4th step is not included on the syringe label or case labeling of Symjepi, the direction to deploy the needle safety guard is already included in the IFU for Symjepi and they did not observe premature deployment of the needle safety guard in the HF validation study.

[h] Response to FDA May 28, 2021 Information Request for Zimhi (NDA 212854). San Diego (CA): Adamis Pharmaceuticals Corporation; 2021 JUN 02. Available from: \\CDSESUB1\evsprod\nda212854\0064\m1\us\response-to-fda-05-28-2021-info-request.pdf

Furthermore, Adamis noted that they consider the addition of the 4th step to be a minimal change as it is not a new instruction. They also concluded that this step along with their proposed training and education program should lead to the proper use and disposal of the product as well as reduce the risk of accidental needlestick injury and transmission of blood borne pathogens. In our IR, we also requested they submit their risk assessment of the proposed changes. In their response, Adamis discussed several design features that reduce the risk of premature deployment of the safety guard (b) (4) . Adamis also noted that there have been no postmarket reports of premature needle deployment or needlesticks for the currently marketed Symjepi product. However, they plan to capture postmarket reports of premature deployment in their pharmacovigilance program.

We reviewed Adamis's response and note that while they have not provided new data to support the addition of the 4th step to the syringe label and case labeling, their proposal to evaluate postmarket reports of premature deployment of the safety guard may be sufficient to allow this application to move toward approval in light of the current public health opioid crisis. Given the public health need for additional naloxone options in the current opioid crisis amid the concurrent Coronavirus Disease 2019 (COVID-19) pandemic, we find that the benefit of having an injectable naloxone hydrochloride prefilled syringe for community use outweighs the risk for unintended consequences that may exist with the proposed changes to the user interface. We agree that an enhanced postmarket pharmacovigilance approach is reasonable and will provide the Agency with useful information once the product is marketed (see also section 3.3 below).

During our evaluation of the labeling, DAAP discussed with DMEPA the potential for adding an image of the Zimhi product with labeled device components to Section 2 of the full prescribing information (FPI). The inclusion of such an image may be useful in facilitating discussions between the healthcare provider and the intended Zimhi user on how to use the product. DMEPA agrees with this inclusion and we provide recommendations in Table 2 below.

3.2 TRAINING

Adamis proposes to implement a training program that will include a training video and trainer device for use by healthcare providers (HCP's) and lay users. The training video will emphasize proper use of the needle guard as well as instruct users to seek medical attention if an accidental needlestick injury occurs. The training program will also include a slide presentation intended for HCP's (physicians, pharmacists), harm-reductionists, social workers, and recovery caregivers to assist in educating users about the proper use of Zimhi. While we certainly encourage training, we note that in the absence of administrative controls, there is no way to ensure that all intended users will receive such training. Furthermore, given the intended use of this product for treating an emergency opioid overdose and the fact that any bystander may be using the product, the likelihood that such training materials will reach the intended user is minimized. As such, relying on training as a risk mitigation measure can be expected to have a limited impact on residual risk.

Adamis provided the draft training program, instructions for use for the trainer device as well as the draft slide presentation. However, we note that Adamis did not provide the draft container and carton labeling for the trainer device. Therefore, on August 10, 2021 we sent an Information Request (IR)[i] to Adamis asking that they submit the container labels and carton labeling for the trainer device as well as 2D images of the intend-to-market trainer device and Zimhi device positioned side-by-side. On August 13, 2021, Adamis submitted the requested images. We reviewed each component from a medication error perspective and identified that the (b) (4) Furthermore, as these training materials will not be part of FDA-approved labeling, we provide recommendations in Table 3 below for Adamis to include consistent instructions/images throughout each training material to ensure consistency with the final, approved labels and labeling.

3.3 PHARMACOVIGILANCE

To detect accidental needlestick injuries that may occur after approval, Adamis proposes a pharmacovigilance program. According to Adamis, their pharmacovigilance program will include safety reporting, medical review, literature monitoring, signal detection, aggregate safety reports, risk-benefit analysis, and risk management plans. Adamis notes that if accidental needlestick injuries are reported, they will consider additional mitigations, such as reminders and additional training. During this review cycle, discussion between the DMEPA, DAAP and Division of Pharmacovigilance (DPV) review teams noted that Adamis's plan may not be adequate to obtain reports of needlesticks. Therefore, it was proposed that a registry may be a more reliable way to collect detailed information about needlestick injuries. Subsequently, DAAP consulted DPV and Division of Epidemiology (DEPI) to review Adamis's proposed pharmacovigilance plan and provide feedback on a proposed registry. At the time of this review, the specifics of the enhanced pharmacovigilance plan are still under discussion and will be addressed under a separate cover.

4 CONCLUSION AND RECOMMENDATIONS

Given the public health need for additional naloxone options in the current opioid crisis amid the concurrent Coronavirus Disease 2019 (COVID-19) pandemic, we find that the benefit of

[i] Response to FDA August 10, 2021 Information Request for Zimhi (NDA 212854). San Diego (CA): Adamis Pharmaceuticals Corporation; 2021 AUG 13. Available from: \\CDSESUB1\evsprod\nda212854\0069\m1\us\response-to-fda-08-10-2021-info-request.pdf

having an injectable naloxone hydrochloride prefilled syringe for community use outweighs the residual risk associated with the user interface design of this product. We find the proposed mitigation strategies from Adamis to be reasonable, though, as discussed above, the training will have limited effect on residual risk. We conclude that an enhanced pharmacovigilance plan should be part of the approval for this drug given the identified difference in risk for transmission of blood borne pathogens between patients for Symjepi and patients for Zimhi. Furthermore, the proposed labels, labeling, and training materials can be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 for the Division and in Section 6 for Adamis Pharmaceuticals Corporation.

5 RECOMMEDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The device term is not consistently presented throughout the prescribing information (i.e. both "prefilled syringe" and "pre-filled syringe" are used). We also note that the device term used elsewhere in labeling (i.e., carton, container, and Instructions for Use) is "prefilled syringe".	To maintain consistency and improve readability, the device term should be the same throughout prescribing information.	Revise the device term so that it is consistent throughout all labels and labeling. For example, prefilled syringe.
2.	The Dosage and Administration, Description and Patient Counseling sections include the package type term (b) (4)	(b) (4) is not a recommended package type term and is inconsistent with the package type term "single dose" that is located elsewhere in the prescribing information (PI)	If OPQ concurs, to maintain consistency with the package type term that is elsewhere in the PI and labeling, we recommend revising the package type term from (b) (4) to "single dose".

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		and on the syringe and carton labeling.	
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The Dosage and Administration section 2.1 *Important Administration Instructions,* includes the statement (b) (4)	This statement does not seem relevant to opioid overdose patients because it is unlikely that the patient would be responsive regardless of age.	We recommend removing this statement from this section.
2.	The Dosage and Administration section 2.1 *Important Administration Instructions* (b) (4)	Re-capping the needle after the cap is removed may increase the risk of accidental needlestick injuries.	Add the following statement as the last bulleted point in section 2.1: "Do NOT attempt to re-cap the needle with the needle cap once it has been removed."
3.	The Dosage and Administration section of the PI (b) (4)	Including a labeled image of the prefilled syringe may facilitate the healthcare provider's discussion with the patient and/or caregiver when providing important administration instructions.	Add an image of the prefilled syringe to section 2 and label each part of the syringe (i.e. needle cap, safety guard, syringe barrel, plunger). Additionally, we recommend retaining the statement that instructs healthcare providers to "Instruct the patient and

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			caregiver to read the *Instructions for Use*…"
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The Dosage Forms and Strengths section (b) (4)	A description of identifying characteristics is required by 21 CFR 201.57(c)(4)(ii) and can be used to help mitigate the risk of administering deteriorated or contaminated drug for this product.	Include that the solution is clear, colorless to slightly yellow. For example: "5 mg Injection: 5 mg/0.5 mL naloxone hydrochloride is a clear, colorless to slightly yellow solution in a single dose prefilled syringe…"
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The case is not consistently presented in the How Supplied/Storage and Handling section (b) (4)	To maintain consistency and minimize the risk for confusion, the case term should be the same throughout this section.	Revise the statement beginning as (b) (4) to "Case containing one (b) (4)
2.	The How Supplied/ Storage and Handling section (b) (4)	These important identifying characteristics of the drug product should be included in the How Supplied section per 21 CFR 201.57(c)(17).	Include that the solution is clear, colorless to slightly yellow in these sections. For example: (b) (4) clear, colorless to slightly yellow solution (b) (4)
Full Prescribing Information – Section 17 Patient Counseling			
1.	The Patient Counseling section includes the statement (b) (4)	This statement does not seem relevant to opioid overdose patients because the patient would not be	We recommend removing this statement from this section.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)	responsive regardless of age.	
Instructions for Use in the Prescribing Information			
2.	The image included under "Get Ready to Use ZIMHI™" associated with the instruction, "ZIMHI™ is injected downwards, into the (b) (4) (as shown), through clothing (b) (4)" illustrates (b) (4)	The injection is intended to be administered to the anterolateral aspect of the thigh. Inconsistency between the image and the intended route of administration could result in wrong site medication errors.	We recommend the image be revised such that it reflects an injection into the anterolateral aspect of the thigh. Also, see recommendation under the header, "Instructions for Use Pull Out" for the Applicant in Table 3 below.
3.	Step 2 of the IFU contains the statement: (b) (4)	This statement does not seem relevant to opioid overdose patients because the patient would not be responsive regardless of age.	We recommend removing this statement from the IFU.
4.	As currently presented, Step 4 "After Use (b) (4) 'Using one hand with fingers behind the needle slide safety guard over needle'" is located several lines down from Step 3.	Users may overlook this step if it is not located immediately after the injection step. If a user does not deploy the safety guard, there is a risk of accidental needlestick injury to the user.	To ensure that users see this important safety step we recommend relocating step 4 so that it is immediately below Step 3.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
5.	The image of the prefilled syringe, located below Step 2 of the IFU, (b) (4)	Including a labeled image of the prefilled syringe in the IFU may help the user to easily identify each part of the syringe during an emergency.	Label each part on the image of the prefilled syringe (i.e. needle cap, safety guard, syringe barrel, plunger).

6 RECOMMENDATIONS FOR ADAMIS PHARMACEUTICALS CORPORATION

Table 3. Identified Issues and Recommendations for Adamis Pharmaceuticals Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Syringe Label			
1.	The route of administration has been omitted from the principal display panel (PDP).	The route of administration is critical information that should be included on the PDP.[j]	Space permitting, add the route of administration to the PDP of the syringe label. For example, "For intramuscular or subcutaneous injection."
2.	The statement "after use call 911" was removed from the syringe label to accommodate the statement "slide down safety guard 4".	This instruction, "after use call 911", should be retained on the syringe label as it is an important step to ensure that the opioid overdose patient receives appropriate medical attention following the use of Zimhi.	Add the statement, "after use call 911" back to the syringe label on the PDP.
Case Labeling			

[j] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Table 3. Identified Issues and Recommendations for Adamis Pharmaceuticals Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The information on the front of the case labeling appears cluttered.	The cluttered appearance may reduce readability and distract from the most important information on the case labeling. (b) (4) more important information, i.e. established name, strength, and instructions for using the prefilled syringe, is less prominently displayed.	To improve readability, consider reducing the prominence of the term, (b) (4) on the case labeling to allow for more space for the more important information. You may also consider removing the term, (b) (4) from the case labeling.
Inner Carton Labeling			
1.	The net quantity is missing from the Principal Display Panel (PDP).	As currently presented, the net quantity, located on the side panel, may be overlooked.	Add the net quantity statement (i.e., Contains Two Syringes) to the PDP.[k]
Syringe Label, Inner Carton Labeling, Outer Carton Labeling			
1.	The total quantity per total volume does not contain a space between the numerical volume and unit of measurement	Lack of space between the numerical volume and unit of measurement may decrease readability.[l]	Add a space between the numerical volume and unit of measurement (i.e., 5 mg/0.5 mL).

[k] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[l] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2019 FEB 07]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 3. Identified Issues and Recommendations for Adamis Pharmaceuticals Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(i.e., 5mg/0.5mL)		
Instructions for Use Pull Out			
1.	The image included under "Get Ready to Use ZIMHI™" associated with the instruction, "ZIMHI™ is injected downwards, into the (b) (4) (as shown), through clothing (b) (4) illustrates (b) (4)	The injection is intended to be administered to the anterolateral aspect of the thigh. Inconsistency between the image and the intended route of administration could result in wrong site medication errors.	Revise the image such that it reflects an injection into the anterolateral aspect of the thigh.
2.	Step 2 of the IFU contains the statement: (b) (4)	This statement does not seem relevant to opioid overdose patients because the patient would not be responsive regardless of age.	Remove this statement from the IFU.
3.	As currently presented, Step 4 "After Use (b) (4) Using one hand with fingers behind the needle slide safety guard over needle" is included on the back side of the Pull Out IFU.	Users may overlook this step if they do not turn over the IFU after giving the injection. If a user does not deploy the safety guard, there is a risk of accidental needlestick injury to the user.	To ensure that users see this important safety step we recommend adding step 4 to the front side of the IFU Pull Out immediately after Step 3. You may consider making the IFU Pull Out longer (lengthwise) to ensure that this important instruction fits on the front of the IFU as well as to ensure that no other information is removed from the front of the IFU.
4.	The IFU contains the statement "For more	The inconsistency may raise confusion.	Revise the phone number to be consistent with the one

Table 3. Identified Issues and Recommendations for Adamis Pharmaceuticals Corporation (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	information about ZIMHI prefilled syringe and proper use of the ZIMHI, call (b) (4) or visit www.ZIMHI.com. However, the IFU included in the PI includes the edited phone number as (b) (4)		included in the IFU within the PI. For example: "For more information about ZIMHI prefilled syringe, call (b) (4) or visit www.ZIMHI.com.
5.	The image of the prefilled syringe, located below Steps 1 and 2 of the IFU, (b) (4)	Including a labeled image of the prefilled syringe in the IFU may help the user to easily identify each part of the syringe during an emergency if the IFU is used.	Label each part on the image of the prefilled syringe (i.e. needle cap, safety guard, syringe barrel, plunger).

General Comments for Training Materials

We reviewed your draft Zimhi Trainer Device labels and labeling, Instructions, training video, and slide presentation and have the following feedback:

1. (b) (4)

2. The statements (b) (4) To improve readability and provide better contrast, we recommend changing the color of the text and/or background for these statements and find a means to make these statements more prominent.

Table 3. Identified Issues and Recommendations for Adamis Pharmaceuticals Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3. 4.	(b) (4)		
5.	Ensure that all instructions and images in all training materials are consistent with the final to-be-marketed instructions on the container labels, carton labeling as well as in the IFU and PI that are approved by the Agency.		

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Zimhi that Adamis Pharmaceuticals Corporation submitted on May 13, 2021.

Table 4. Relevant Product Information for Zimhi	
Initial Approval Date	N/A
Active Ingredient	Naloxone hydrochloride
Indication	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression
Route of Administration	Intramuscular and subcutaneous
Dosage Form	injection
Strength	5 mg/0.5 mL
Dose and Frequency	5 mg intramuscular/subcutaneous into thigh; additional doses may be administered every 2 to 3 minutes until emergency medical assistance arrives.
How Supplied	Carton containing two (naloxone hydrochloride injection, USP) 5 mg/0.5 mL prefilled syringes.
Storage	Store at controlled room temperature 15°C to 25°C (59°F to 77°F), excursions permitted.
Container Closure	Prefilled syringe

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 17, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, naloxone hydrochloride and injection. Our search identified 9 previous reviews[m,n,o,p,q,r,s,t,u], and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. – N/A

APPENDIX D. – N/A

APPENDIX E. INFORMATION REQUESTS

We sent an Information Request (IR) to Adamis on May 28, 2021 to request data to support the labeling revisions from the previous review cycle. The IR response can be accessed in EDR via:

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[m] Borders-Hemphill. Label and Labeling Review for naloxone hydrochloride (NDA 205787). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 DEC 11. RCM No.: 2013-1727.

[n] Shah, M. Human Factors Study Results Review Memo for Evzio (NDA 205787). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 25. RCM No.: 2015-1538.

[o] Shah, M. Postmarket Medication Error Review for Evzio (NDA 205787). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 DEC 28. RCM No.: 2015-2427.

[p] Calderon, M. Label and Labeling Review for Evzio (NDA 205787/S007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 SEP 22. RCM No.: 2016-940.

[q] Schlick, J. Postmarket Medication Error Review for Evzio (NDA 209862). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 12. RCM No.: 2017-2439.

[r] Shah, M. Human Factors and Label and Labeling Review for Evzio (NDA 209862/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 07. RCM No.: 2018-2805.

[s] Flint, J. URRA and CA and Label and Labeling Review for Zimhi (NDA 212854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 24. RCM No.: 2019-8 and 2019-15.

[t] Flint, J. URRA Label and Labeling Review for Narcan (NDA 213643). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 25. RCM No.: 2019-2036 and 2019-2037.

[u] Johnson, C. Label and Labeling Review for Zimhi (NDA 212854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 04. RCM No.: 2019-8-1.

\\CDSESUB1\evsprod\nda212854\0064\m1\us\response-to-fda-05-28-2021-info-request.pdf

We sent an IR to Adamis on August 10, 2021 to request draft labels and labeling for their trainer device as well as 2D images of the trainer device positioned side-by-side with the Zimhi device. The IR response can be accessed in EDR via:

\\CDSESUB1\evsprod\nda212854\0069\m1\us\response-to-fda-08-10-2021-info-request.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[v] along with postmarket medication error data, we reviewed the following Zimhi labels and labeling submitted by Adamis Pharmaceuticals Corporation.

- Zimhi Safety Label submitted on 5/13/2021
- Zimhi Actuator Label submitted on 5/13/2021
- Zimhi Syringe Label submitted on 5/13/2021
- Zimhi Syringe Case Labeling submitted on 5/13/2021
- Zimhi Inner Carton Labeling submitted on 5/13/2021
- Zimhi Outer Carton Labeling submitted on 5/13/2021
- Zimhi Instructions for Use Pull Out (Image not shown) submitted on 5/13/2021 can be accessed in EDR via:
    - \\CDSESUB1\evsprod\nda212854\0063\m1\us\draft-carton-container-labels.pdf
- Zimhi Prescribing Information and Instructions for Use (Image not shown) submitted on 6/2/2021 can be accessed in EDR via:
    - \\CDSESUB1\evsprod\nda212854\0063\m1\us\draft-labeling-text.docx
- Trainer Device Safety Label submitted on 8/13/2021
- Trainer Device Actuator Label submitted on 8/13/2021
- Trainer Syringe Label submitted on 8/13/2021
- Trainer Device Reset Label submitted on 8/13/2021
- Trainer Case Labeling submitted on 8/13/2021
- Trainer Device Carton Labeling submitted on 8/13/2021
- Trainer Device Instructions for Use submitted on 8/13/2021
- 2D images of Trainer Device and Zimhi device side-by-side 8/13/2021

F.2 Labels and Labeling Images

Safety Label

[v] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Use Review – Brief

Date:	August 4, 2021
Reviewer:	Yuze Yang, Pharm.D. Drug Utilization Analyst Division of Epidemiology II (DEPI II)
Team Leader:	Corinne Woods, MPH, RPh Drug Utilization Analysis Team Leader DEPI II
Division Director:	Rajdeep Gill, Pharm.D. Deputy Director for Drug Utilization DEPI II
Subject:	Symjepi utilization in the outpatient retail setting
Product Names:	Symjepi (epinephrine injection)
Application Type/Number:	NDA 207534
Applicant/Sponsor:	Adamis Pharmaceuticals Corp.
OSE RCM #:	2021-1445

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

1 INTRODUCTION

In June of 2017, the FDA granted an approval to NDA 207534 from Adamis Pharmaceuticals, Inc (applicant) for Symjepi, a pre-filled syringe containing epinephrine 0.3 mg/0.3 mL solution indicated for emergency treatment of allergic reactions. The delivery device for this product is different from epinephrine auto-injectors (EAIs) as it does not leverage any spring-loaded mechanism, is smaller, and utilizes a thinner needle.[1]

In 2021, The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) has received a class 2, resubmission new drug application (NDA) 212854 (Zimhi® naloxone injection) application via 505(b)(2) regulatory pathway from the same applicant. This naloxone injectable solution leverages the same kind of delivery device with which the FDA had already developed some familiarity from the previous Symjepi approval. Thus, to understand the safety of this injection delivery device for naloxone, DAAP initially requires an estimate of how many Symjepi prescriptions have been distributed via outpatient retail and mail-order pharmacies since its approval and its subsequent commercial introduction in 2019.

2 METHODS AND MATERIALS

The Agency used proprietary databases available to conduct these drug utilization analyses. See **Appendix A** for full database descriptions. We used the IQVIA National Sales Perspectives™ (NSP) database to determine the distribution of sales among various settings of care where Symjepi was sold by manufacturers to various channels of distribution from January 2019 through June 2021. Subsequently, we leveraged IQVIA National Prescription Audit™ (NPA) database to obtain the nationally estimated number of prescriptions for Symjepi syringes dispensed, as well as NSP to obtain the nationally estimated number of units for Symjepi syringes dispensed from all U.S. health care settings from the aforementioned time period.

3 RESULTS

3.1 SETTINGS OF CARE

From January 2019 to June 2021, sales data indicated (b) (4) This drug use evaluation focused on analyzing dispensed prescriptions from the retail and mail-order pharmacy settings; data from non-retail settings were not included in the analysis.

3.2 Manufacturer Sales Data

Table 3.2.1 below provides the nationally estimated number of injections for the Symjepi pre-filled syringes sold from manufacturers to all settings of care. The earliest records of Symjepi injections identified in the database are from January of 2019.

[1] Symjepi (epinephrine) Injection. https://www.symjepi.com/for-healthcare-professionals.php. Accessed July 30, 2021.

Table 3.2.1 – Nationally-estimated number of Symjepi injections sold annually from manufacturers to all U.S. health care settings from January 2019 through June 2021.

	2019 Injections	2020 Injections	Jan – Jun 2021 Injections	Total Injections Jan 2019 – Jun 2021
SYMJEPI	[redacted] (b) (4)			

Source: IQVIA National Sales Perspectives™. Data time period: January 2019 – June 2021. Data extracted Aug 2021. File name: Symjepi - Sales (NSP)_1_Aug-03-2021.xlsx

3.3 Outpatient: Prescription Data

Table 3.3.1 below provides the nationally estimated number of dispensed prescriptions for Symjepi from U.S. outpatient retail and mail-order pharmacies from January 2019 to June 2021. A total of approximately [redacted] (b) (4) prescriptions have been dispensed during this time frame.

Table 3.2.2 – Nationally-estimated number of prescriptions for Symjepi dispensed from U.S. outpatient retail and mail-order pharmacies from January 2019 through June 2021.

	2019 Prescriptions	2020 Prescriptions	Jan – Jun 2021 Prescriptions	Total Prescriptions Jan 2019 – Jun 2021
SYMJEPI	[redacted] (b) (4)			

Source: IQVIA National Prescription Audit™. Data time period: January 2019 – June 2021. Data extracted July 2021. File name: SYMJEPI - Rx (NPA)_1_Jul-29-2021.xlsx

5. DISCUSSION AND LIMITIATIONS

[redacted] (b) (4)

The drug utilization findings from this review should be interpreted in the context of the known limitations of the database used. This review provides national estimates for how much of the Symjepi brand product is being dispensed, but no statistical tests of significance were performed using these data. Therefore, all changes over time should be considered approximate. In addition, these results are only generalizable to the U.S. outpatient retail and mail-order pharmacy settings, and thus do not necessarily represent non-retail setting such as hospitals or ambulatory clinics.

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Data vendor cleared 8/4/2021

RAJDEEP K GILL
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POSTMARKET MEDICATION ERROR REVIEW

U.S. Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of Surveillance and Epidemiology (OSE)
Office of Medication Error Prevention and Risk Mitigation (OMEPRM)
Division of Medication Error Prevention and Analysis (DMEPA)

DATE:	August 3, 2021
TO:	**Max Lerman, PhD, Lead Reviewer, CDRH** **Rumi Young, M.S. RAC., Acting Assistant Director, Injection Devices, CDRH**
SUBJECT:	CDRH Inter-Center Consult Request (ICCR) # 00732951: Safety signal analysis for possible needle stick injury for Symjepi, NDA 207534 and DMEPA's response to questions from CDRH pertaining to their review of Zimhi, NDA 212854
FROM:	Cameron Clark, PharmD, Safety Reviewer, DMEPA 1 Valerie Vaughan, PharmD, Safety Reviewer Team Lead, DMEPA 1 Irene Z. Chan, PharmD, BCPS, Division Director (Acting), DMEPA 1
Safety Reviewer, DMEPA 1	Cameron Clark, Pharm D Signature: Proxy for Cameron Clark
Safety Reviewer Team Lead, DMEPA 1	Valerie S. Vaughan, PharmD Signature:
Division Director (Acting), DMEPA 1	Irene Z. Chan, PharmD, BCPS Signature:

Reference ID: 4876589

1 PURPOSE

This document provides our responses to an Inter-Center Consult Request[a] from CDRH. CDRH requested that we conduct a safety signal analysis for Symjepi focusing on needle stick injury, safety, and failure to deploy the safety guard. CDRH requested our analysis include the contributing factors which resulted in a needle stick injury or close call of needle stick injury in the marketplace for the current device platform to help inform their review of Zimhi (naloxone) injection NDA 212854. Zimhi is a drug-device combination product currently under review that uses the same device platform as the prefilled syringe device constituent part for Symjepi (epinephrine) injection. Both products require manual activation of the needle safety guard to cover the needle after injection, which may pose an increased risk of needle stick injury when compared to a passive (automatic) needle guard feature. Thus, CDRH has requested our assessment of needle stick injuries reported to FDA with the Symjepi device to help inform CDRH's review of the Zimhi device.

In their consult request, CDRH also includes comments related to the previous Symjepi Human Factors (HF) validation study report and a possible discrepancy in technique to deploy the needle safety guard when comparing the Zimhi and Symjepi user interfaces. CDRH requested that we address their comments in our analysis. Therefore, in addition to our analysis of postmarket reports of needle stick injuries associated with Symjepi, we have also provided our response to CDRH's comments on the Symjepi HF report and comparison of Zimhi to Symjepi user interfaces.

2 PRODUCT INFORMATION

2.1 PRODUCT INFORMATION

Table 1. Relevant Product Information for Zimhi[b] (source: Electronic Document Room) and Symjepi (source: labels.fda.gov)

Product Name	Zimhi (naloxone hydrochloride) injection	Symjepi (epinephrine) injection
NDA	212854	207534
Applicant	Adamis	Adamis
Initial FDA Approval Date	Under review	June 15, 2017

[a] The CDRH consult request (ICCR# 00732951) is available at: https://force-dsc.my.salesforce.com/500t000000nQRCd.

[b] The Zimhi proposed Prescribing Information can be accessed in EDR via the following link: \\CDSESUB1\evsprod\nda212854\0063\m1\us\draft-labeling-text.docx

Reference ID: 4876589

Table 1. Relevant Product Information for Zimhi[b] (source: Electronic Document Room) and Symjepi (source: labels.fda.gov)		
Product Name	Zimhi (naloxone hydrochloride) injection	Symjepi (epinephrine) injection
Indication	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients	Emergency treatment of allergic reactions (Type 1) including anaphylaxis
How Supplied	• 5 mg/0.5 mL single dose prefilled syringe	• 0.15 mg/0.3 mL single dose prefilled syringe • 0.3 mg/0.3 mL single dose prefilled syringe
Images of the syringe label and case labeling	Syringe label (front and back) (b) (4) Case labeling (front and back) (b) (4)	Syringe label (front and back) Case labeling (front and back)

3 ANALYSIS OF POSTMARKET REPORTS OF NEEDLE STICK INJURIES ASSOCIATED WITH SYMJEPI

CDRH requested that we evaluate the occurrence rate and total number of instances of needle safety/sharps concerns raised for Symjepi with a specific focus on the following details:

a. The number of Needle Stick with Symjepi since approval.

b. The number of failures to activate needle safety with Symjepi since approval.

c. For a and b, a breakdown of who the user was (pediatric, adult, elderly) and handedness (1 hand or 2 hands to deploy the shield), if that is noted.

d. The resulting harms observed/noted associated with needle sticks (was anyone infected? Were these self-sticks? Were they injecting another individual)?"

We did not identify any safety reports that describe needle stick injury or medication errors in the FDA Adverse Event Reporting System (FAERS) database (for date range: initial approval to 06/29/2021) or in the Symjepi Periodic Adverse Drug Experience Reports (PADER) (for date range: initial approval to 06/14/2020). We also reviewed the Symjepi annual reports (for date range: initial approval to 6/14/2020) and found that Symjepi has been distributed since 2018 with no reports of medication error received by the Agency. Appendix A provides the methods used to search FAERS and the Periodic Adverse Drug Experience Reports and Drug Utilization Data since approval.

Furthermore, On 07/01/2021, we issued a follow up Information Request (IR) to Adamis to request an update on the number of needle stick injuries and complaints related to the potential for needle stick injuries with Symjepi. We sent the follow-up IR in response to Adamis's response received on 10/07/2020 that stated, "No sharp injuries have been reported for Symjepi to date."[c]

Our review of Adamis's response received on 07/09/2021[d] found that:

- Adamis searched their Symjepi Pharmacovigilance (PV) database as well as FDA's FAERS database from initial marketing approval, 15Jun2017, to 01Jul2021
- There were zero reports of needle-stick injuries for the reporting period
- There were zero complaints related to the potential for needlestick injuries for the reporting period
- There were zero failures to activate the sharps injury prevention feature (needle guard)

[c] Re: NDA 212854 Response to Information Request. San Diego (CA): Adamis Pharmaceutical Corporation. 2020 OCT 7. Available from: \\CDSESUB1\evsprod\nda212854\0057\m1\us\response-to-fda-9-23-2020-info-request.pdf.

[d] Re: NDA 212854 Response to Information Request. San Diego (CA): Adamis Pharmaceutical Corporation. 2021 JUL 9. Available from: \\CDSESUB1\evsprod\nda212854\0067\m1\us\response-to-fda-07-01-2021-info-request.pdf.

- As there were zero reports of needlestick injuries/complaints, there was no data on user age, handedness, adverse events or outcomes

4 ASSESSMENT OF CDRH COMMENT REGARDING SYMJEPI HF STUDY REPORT

In their request, CDRH noted that "deployment of the needle shield (i.e. safety guard) was not assessed as a critical task in the Symjepi HF Summary report and that subjects in the study raised concerns regarding the safety guard." We note that "deployment of needle shield (i.e. safety guard)" was assessed *by the sponsor* as a non-critical task in the Symjepi HF report and that not all participants deployed the safety guard. In the Symjepi HF validation study report, some subjects noted "Guard did not easily move, hesitant to try harder for fear of slipping and getting a needle stick." In DMEPA's prior evaluation of Symjepi, we did take into consideration the observed use errors and feedback from subjects noting concerns with the safety guard. However, in that particular case, we ultimately determined the residual risk was acceptable after further discussions with the clinical review division and in light of the overall benefit risk considerations at that time.

5 ASSESSMENT OF CDRH COMPARISION OF SYMJEPI AND ZIMHI USER INTERFACES

In their request, CDRH noted that there was a difference between the indicated patient population for Zimhi (ages 0 to infinity) and the user population that was evaluated in the Symjepi HF Summary report (ages 12 to 64 years old). Our review of the user populations for both products, identified that the intended users (person administering the drug/operating the prefilled syringe device) is the same between Zimhi and Symjepi, that is, the intended users are persons as young as 12 years of age and up. Additionally, CDRH noted that the incidence rate of needle sticks may be related to the user population and who is likely to report such actions and actually use the device. As noted above, we have no reports of use errors associated with the needle guard or needle stick injury. Therefore, we have no data to support any potential differences in the incidence rate that may stem from any differences in user populations.

(b) (4)

We reviewed the approved Instructions for Use (IFU)[e] for Symjepi as well as the proposed IFU for Zimhi that is currently under review. Our review revealed that both IFUs instruct the user to "Using one hand with fingers behind the needle slide safety guard over needle." We also reviewed the instructional videos included in the consult request. We note that the

[e] Symjepi [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. DEC 2020. [cited 2021 JUN 30]. Available from: https://www.accessdata.fda.gov/spl/data/683751b5-3deb-4292-b7e8-96f68bd09f0e/683751b5-3deb-4292-b7e8-96f68bd09f0e.xml

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6 CONCLUSION

Our review of FAERS, the Symjepi PSRs, and Adamis's response to our IR dated 7/1/2021 did not identify any reports of needlestick injury or medication errors with the use of Symjepi. There are limitations to our analysis since medication errors are underreported (the reporting of medication errors to FAERS is voluntary); therefore, our evaluation is not intended to suggest that no medication errors exist in the market for Symjepi.

Appendix A. Review of FDA Adverse Event Reporting System (FAERS) Cases, Periodic Safety Reports, and Drug Utilization Data

A.1 FAERS

On 06/29/2021, using the search criteria and methods provided in the table below, we didn't identify any Symjepi cases associated with needle sticks or medication errors.

FAERS* Search Criteria, Number of Cases Retrieved, and Methods		
Search Criteria	**Search 1**	**Search 2**
Initial FDA Receive Dates:	01Jun2017- 29Jun2021	
Product Name:	Symjepi	---
Product Active Ingredient (PAI):	---	EPINEPHRINE,EPINEPHRINE BITARTRATE,EPINEPHRINE HYDROCHLORIDE
Event:	--- (all events)	--- (all events)
Country (Derived):	USA	USA
Number of Cases Retrieved:	0	3,820
Methods	---	The 3,820 cases were downloaded to Excel and text-searched for mention of "Symj", "Adamis", (b) (4) (b) (4) and "207534"
Number of Cases Identified That Involve Symjepi Needle Sticks or Medication Errors	0	0

*More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

A.2 Periodic Safety Reports

Depending on reporting requirements and waivers, FAERS may contain a subset of cases listed in the Periodic Safety Report (PSR). Thus, on 06/29/2021, we reviewed the 11 PSRs (all submitted quarterly, and using the Periodic Adverse Drug Experience Report [PADER] format) submitted by Adamis for Symjepi. The 11 PSRs indicated that Adamis had not received any reports with "reportable adverse events".

A.3 DRUG UTILIZATION

Table 2 below provides Symjepi annual distribution (excerpted from the Symjepi Annual Reports).

Table 2. Symjepi distribution (source: Symjepi Annual Reports, 2017-2020[f])				
Source	**Description**	**2019-2020**	**2018-2019**	**2017-2018**
				(b) (4)

[f] The 2017-2020 Symjepi Annual Reports are available in docuBridge at: \\CDSESUB1\evsprod\nda207534\0049\m1\us\113-annual-report\distribution-data-ar-15june2017-14june2018.pdf, \\CDSESUB1\evsprod\nda207534\0064\m1\us\113-annual-report\distribution-data-ar-15june2018-14june2019.pdf, and \\CDSESUB1\evsprod\nda207534\0077\m1\us\113-annual-report\distribution-data-ar-15june2019-14june2020.pdf.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 5, 2021
To:	Swati Patwardhan Regulatory Project Manager **Division of Anesthesiology, Addiction, and Pain Medicine (DAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ZIMHI (naloxone hydrochloride injection)
Dosage Form and Route:	prefilled syringe for intramuscular or subcutaneous use
Application Type/Number:	NDA 212854
Applicant:	Target Health LLC

1 INTRODUCTION

On May 15, 2020, Target Health LLC submitted for the Agency's review a resubmission of their New Drug Application (NDA) 212854 for ZIMHI (naloxone hydrochloride injection). The Agency issued a Complete Response (CR) letter to the Applicant on November 22, 2019. The proposed indication is for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients. ZIMHI is intended for immediate administration as emergency therapy in settings where opioids may be present. ZIMHI is not a substitute for emergency medical care.

On May 31, 2020, the Division of Anesthesiology, Addiction, and Pain Medicine Products (DAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ZIMHI (naloxone hydrochloride injection).

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ZIMHI (naloxone hydrochloride injection).

2 CONCLUSIONS

Due to outstanding clinical and device deficiencies, DAAP has issued a Complete Response (CR) letter dated November 13, 2020. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Office of New Drugs, ORPURM
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Version Date:	November 7, 2020
From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	John J. Alexander, MD, MPH, Deputy Director DPMH
NDA Number:	212,854
Sponsor:	Adamis Pharmaceuticals
Drug:	Naloxone Hydrochloride (proposed commercial name: Zimhi)
Indication:	Emergency treatment of known or suspected opioid overdosage
Dosage Form and Route of Administration:	Injection for intramuscular (IM) or subcutaneous (SC) use
Dosing regimen:	"Administer to adult or pediatric patients into the anterolateral aspect of the thigh, through clothing if necessary." "Additional doses of may be given every 2 to 3 minutes until emergency medical assistance arrives."
Division Consult Request:	The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requests DPMH assistance in reviewing section 8.4 (Pediatric Use) of labeling for this 505(b)(2) application relying on Narcan as the reference listed drug.

Background

This review supports retention of a specific paragraph of concern in section 8.4 of labeling for the candidate naloxone hydrochloride product (NDA 212,854; Zimhi). Zimhi is single-agent naloxone hydrochloride drug intended as a treatment for known or suspected opioid overdose. [The review does not discuss naloxone containing combination products (e.g., buprenorphine/naloxone) intended, for example, for treatment of opioid dependence.]

Naloxone HCl was first approved in 1971 (Narcan, NDA 16,636), for intravenous (IV), IM, and SC administration. Since that time, multiple single agent naloxone products have been approved as NDAs and ANDAs. Products are available for IV, IM, SC and nasal administration.

The candidate product is intended for emergency intervention for known or suspected opioid overdose and may be available for use outside of hospital settings. Use scenarios could include, for example, emergency response teams arriving on scene, patients fearing onset of overdose, or other persons who suspect overdose in patients and who intend to provide naloxone per labeled instructions pending arrival of emergency response personnel. The candidate product is relying upon Narcan as a reference product under provision of the 505(b)(2) drug review process.

DAAP requests DPMH-Pediatric assistance in reviewing a specific proposed paragraph in section 8.4 (Pediatric Use) of the candidate product. (b) (4)

(b) (4)

At the November 5, 2020 team meeting the consensus between DAAP, DPMH and other participants was that the paragraph of concern referred to general non-product specific information that would be applicable to any single agent naloxone product and could be retained in candidate labeling.

The proposed language for section 8.4 is presented below. The paragraph of concern is italicized. The rationale for supporting retention of the paragraph in question follows thereafter.

Labeling

8.4 Pediatric Use

The safety and effectiveness of ZIMHI ™ (for intramuscular and subcutaneous use) have been established in pediatric patients of all ages for the emergency treatment of known or suspected opioid overdose. Use of naloxone hydrochloride in all pediatric patients is supported by adult bioequivalence studies coupled with evidence from the safe and effective use of another naloxone hydrochloride injectable product. No pediatric studies were conducted for ZIMHI ™.

Absorption of naloxone hydrochloride following subcutaneous or intramuscular administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds appropriately to naloxone hydrochloride injection, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.

Reference ID: 4698757

In opioid-dependent pediatric patients, (including neonates), administration of naloxone hydrochloride may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. *There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. Unlike acute opioid withdrawal in adults, acute opioid withdrawal in neonates manifesting as seizures may be life-threatening if not recognized and properly treated. Other signs and symptoms in neonates may include excessive crying and hyperactive reflexes. In these settings where it may be preferable to avoid the abrupt precipitation of acute opioid withdrawal symptoms, consider use of an alternative, naloxone hydrochloride product that can be dosed according to weight and titrated to effect. [see Warnings and Precautions (5.3)].*

In pediatric patients under the age of one year, the caregiver should pinch the thigh muscle while administering ZIMHI ™. Carefully observe the administration site for evidence of residual needle parts, signs of infection, or both. [see Dosing Information (2.2)].

Discussion

At the November 5, 2020 team meeting, DPMH and DAAP acknowledged and agreed that the passage of concern contains safety information that is non-product-specific and is readily available.

The language of the first and fourth italicized sentences recommending against abrupt precipitation of opioid withdrawal in neonates and the use of alternative drugs is described in neonatal practice guidelines. [1,2,3] The second and third italicized sentences describing signs and symptoms of neonatal opioid exposure is included in a variety of readily available neonatal and pediatric reference texts.[4,5,6] This information describes safety concerns related to the risk of abrupt opioid withdrawal from administration of naloxone products.

In conclusion, DAAP and DPMH agree the paragraph in question is non-product-specific, provides important safety information for pediatric use, and should be retained in labeling for the candidate product.

[1] Siu A, Robinson A. Neonatal Abstinence Syndrome: Essentials for the Practitioner. J Pediatr Pharmacol Ther. 2014;19(3):147–155.
[2] Australasian Neonatal Medicines Formulary (ANMF) Consensus Group. Naloxone: Newborn use only. https://www.slhd nsw.gov.au/RPA/neonatal%5Ccontent/pdf/guidelines/Naloxone_ANMFv1.0_Full_20181016.pdf; website accessed November 6, 2020.
[3] Patrick SW, Barfield WD, Poindexter BB, et al. Neo natal Opioid Withdrawal Syndrome. Pediatrics. November 2020. 164(5): e2020029074.
[4] Mardante KJ, Kliegman RM. Nelson's Essentials of Pediatrics, 8th Ed. 2019. Elsevier. Philadelphia PA, USA. pp: 90 and 235.
[5] Gomella TL. Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs, 5th Ed. 2004. Lange Medical Books/McGraw Hill, New York NY, USA. pp: 426-429.
[6] Kleinman K, McDaniel L, Molloy M. The Harriet Lane Handbook, 22nd Ed. 2021. Elsevier. Philadelphia PA, USA. pp: 464-465.

Reference ID: 4698757

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/s/

ETHAN D HAUSMAN
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JOHN J ALEXANDER
11/09/2020 08:42:17 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 4, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 212854
Product Name and Strength:	Zimhi (naloxone HCL) Injection, 5 mg/0.5 mL
Applicant/Sponsor Name:	Adamis Pharmaceuticals Corporation (Adamis)
OSE RCM #:	2019-8-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Safety Evaluator:	Zahra Farshneshani, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information, instructions for use, container labels and carton labeling received on September 30, 2019, July 31, 2020 and August 14, 2020 for Zimhi. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised labeling for Zimhi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

1.1 REGULATORY HISTORY

Adamis originally submitted their NDA on December 31, 2018. However, a Complete Response letter was issued to Adamis on November 22, 2019 due to nonclinical deficiencies. Adamis submitted their complete response to the clinical deficiencies on May 15, 2020.

[a] Flint J and Johnson C. Use-Related Risk Analysis, Comparative Analyses, Label and Labeling Review for Zimhi (NDA 212854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 24. RCM No.: 2019-8 and 2019-15.

Reference ID: 4697382

2 CONCLUSION

The revised prescribing information, container labels and carton labeling are unacceptable from a medication error perspective. In Section 3 below, Tables 1 and 2 include the identified medication error issues with the submitted revised labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

3 RECOMMENDATIONS

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for DAAP			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information - General Issues			
1.	The device is not consistently presented throughout the prescribing information (i.e. both "prefilled syringe" and "pre-filled syringe" are used). We also note that the device term used elsewhere in labeling (i.e., carton, container, and Instructions for Use) is "prefilled syringe".	To maintain consistency the device should be the same throughout prescribing information.	Revise the device term so that it is consistent throughout all labels and labeling. For example, prefilled syringe.
Full Prescribing Information			
1.	Dosage and Administration section, Description section and Patient Counseling section includes package type term as (b) (4) injection.	(b) (4) is not a recommended package type term and is inconsistent with the package type term "single dose" that is located elsewhere in the prescribing information (PI) and on the syringe and carton labeling.	If OPQ concurs, to maintain consistency with the package type term that is elsewhere in the PI and labeling, revise (b) (4) to "single-dose".

2.	The Dosage and Administration section and Patient Counseling section includes the statement (b) (4)	This statement does not seem relevant to opioid overdose patients because the patient would not be responsive regardless of age.	Remove this statement from the IFU.
3.	The Dosage Forms and Strengths section and the How Supplied section (b) (4)	These important identifying characteristics of the drug product should be included in the Dosage Forms and Strengths section per 21 CFR 201.57(c)(4)(ii). Furthermore, this information should be included in the How Supplied section per 21 CFR 201.57(c)(17).	Include that the solution is clear in these sections. For example, in the Dosage Forms and Strengths section: "5 mg Injection: 5 mg/0.5 mL naloxone hydrochloride is a clear (b) (4) In the How Supplied section: (b) (4)
4.	In the How Supplied section, the NDC (National Drug Code) for the outer carton labeling is missing.	All assigned NDC numbers should be listed in the How Supplied section.	Add the outer carton labeling NDC to the How Supplied section.
Instructions for Use in the Prescribing Information			
5.	The image included under "Get Ready to Use ZIMHI™" associated with the instruction, "ZIMHI™ is injected downwards,	The injection is intended to be administered to the anterolateral aspect of the thigh.	This inconsistency between the image and the intended route of administration could result in wrong site medication errors. Inform the

	into the (b) (4) (as shown), through clothing (b) (4) illustrates (b) (4)		Applicant to revise the image such that it reflects an injection into the anterolateral aspect of the thigh. Also, see recommendation under the header, "Instructions for Use Pull Out" for the Applicant in Table 3 below.
6.	Step 2 of the IFU contains the statement: (b) (4)	This statement does not seem relevant to opioid overdose patients because the patient would not be responsive regardless of age.	Remove this statement from the IFU.

Table 2. Identified Issues and Recommendations for Adamis (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Inner Carton Labeling			
1.	Net quantity is missing from the Principal Display Panel (PDP).	Missing net quantity statement may result in confusion.	Add the net quantity statement (i.e., Contains Two Syringes) to the PDP.[b]
Outer Carton Labeling			
1.	The format of the expiration date has been omitted from the outer carton labeling.	The use of confusing expiration date formats has led to misinterpretation and deteriorated drug medication errors.	To minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

			expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Case Labeling			
1.	The route of administration has been omitted from the PDP.	The route of administration is critical information that should be included on the PDP.[c]	Add the route of administration, for intramuscular or subcutaneous injection, to the PDP of the case label.
Syringe Label			
1.	The route of administration has been omitted from the PDP.	The route of administration is critical information that should be included on the PDP.[d]	Space permitting, add the route of administration to the PDP of the syringe label. For example, "For intramuscular or subcutaneous injection."
Syringe Label, Inner Carton Labeling, Outer Carton Labeling			

[c] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[d] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

2.	The total quantity per total volume does not contain a space between the numerical volume and unit of measurement (i.e. 5 mg/0.5mL)	Missing space between the numerical strength and unit of measurement may decrease readability.[e]	Add a space between the numerical volume and unit of measurement.
Instructions for Use Pull Out			
1.	The image included under "Get Ready to Use ZIMHI™" associated with the instruction, "ZIMHI™ is injected downwards, into the (b) (4) (as shown), through clothing (b) (4) illustrates (b) (4)	The injection is intended to be administered to the anterolateral aspect of the thigh.	This inconsistency between the image and the intended route of administration could result in wrong site medication errors. Please revise the image such that it reflects an injection into the anterolateral aspect of the thigh.
2.	Step 2 of the IFU contains the statement: (b) (4)	This statement does not seem relevant to opioid overdose patients because the patient would not be responsive regardless of age.	Remove this statement from the IFU.

[e] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2019 FEB 07]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

APPENDIX A. LABELS AND LABELING

A. List of Labels and Labeling Reviewed and Images

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following naloxone labels and labeling submitted by Adamis.

- Safety Label received on September 30, 2019
- Actuator Label received on September 30, 2019
- Syringe Label received on September 30, 2019
- Syringe Case Labeling received on September 30, 2019
- Inner Carton Labeling received on July 31, 2020
- Outer Carton Labeling received on July 31, 2020
- Instructions for Use Pull Out received on September 30, 2019 and can be accessed in EDR via:
  - \\CDSESUB1\evsprod\nda212854\0038\m1\us\draft-carton-container-labels.pdf
- Prescribing Information and Instructions for Use (Image not shown) received on August 14, 2020 and can be accessed in EDR via:
  - \\CDSESUB1\evsprod\nda212854\0051\m1\us\draft-labeling-text-track-changes.docx
-

(b) (4)

[redacted]

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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11/05/2020 04:12:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 10/23/2020 **Date consulted:** 10/21/2020

From: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Anesthesia and Addiction Products

Drug: Zimhi (naloxone hydrochloride) injection for intramuscular or subcutaneous use

NDA: 212854

Applicant: Adamis Pharmaceuticals Inc

Subject: Pregnancy and Lactation Labeling Recommendations

Indication: Treatment of known or suspected opioid overdose

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 212854
- DPMH consult request dated 10/21/20, DARRTS Reference ID 4689593
- DPMH review of Narcan (naloxone) Nasal Spray, NDA 208411. Suchitra Balakrishnan, MD, PhD. September 28, 2015. DARRTS Reference ID 3834852[1]

Consult Question: "Input requested to the proposed language in section 8.

[1] The Narcan review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

Reference ID: 4691494

INTRODUCTION AND BACKGROUND

Regulatory History

- Naloxone has been approved since 1971. Currently, naloxone is available as a prefilled autoinjector at a dose of 2mg and as a nasal spray containing 4mg of naloxone.
- On December 31, 2018, the applicant, Adamis Pharmaceuticals, submitted a 505(b)(2) new drug application for naloxone hydrochloride injection, 5 mg/0.5ml, prefilled injector.
- The FDA issued a Complete Response (CR) letter on November 22, 2019 due to product quality, nonclinical and clinical pharmacology deficiencies.
- The applicant responded to the CR letter on May 15, 2020.
- DAAP consulted DPMH on October 21, 2020 to assist with the Pregnancy and Lactation subsections of labeling.

Naloxone Drug Characteristics[2]

Drug class	Naloxone hydrochloride is an opioid antagonist
Mechanism of action	Naloxone antagonizes the opioid effect by competing for the same receptor sites
Dose and administration	Administered as a single dose for patient with known or suspected opioid overdose. Additional doses may be given every 2 to 3 minutes until emergency assistance arrives.
Molecular weight	(b) (4) g/mol
Half-life	1.5 hours
Plasma protein binding	Occurs but is relatively weak
Warnings and precautions	Precipitation of severe opioid withdrawal

REVIEW

PREGNANCY

Nonclinical Experience

In animal reproduction studies, no embryotoxic or teratogenic effects were observed in mice and rats treated with naloxone hydrochloride during the period of organogenesis at doses equivalent to 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg

The reader is referred to the Pharmacology/Toxicology review by Carlic Huynh, Ph.D., for further details.

Pharmacovigilance (PV) Database

There were no confirmed pregnancies during the clinical development program.

DPMH Review of Literature

DPMH had previously reviewed naloxone in September 2016,[3] and in that review DPMH noted that naloxone rapidly crosses the placenta and there is the potential for fetal and maternal opioid withdrawal with naloxone. The reader is referred to the 2016 DPMH review of naloxone for details of the publications that were reviewed.

[2] Applicant's proposed labeling for Zimhi **(**naloxone hydrochloride) injection

[3] DPMH review of Narcan (naloxone) Nasal Spray, NDA 208411. Suchitra Balakrishnan, MD, PhD. September 28, 2015. DARRTS Reference ID 3834852

Reference ID: 4691494

DPMH conducted a brief search of published literature from 2016 to present using the search terms "naloxone" and "pregnancy" and "congenital defects/congenital anomalies/teratogenicity/prematurity/stillbirth/spontaneous abortion/miscarriage" and did not identify any new publications related to these search terms. Although there are numerous publications regarding "opioid overdose and pregnancy," there were two publications regarding naloxone and opioid overdose in pregnancy. However, the full articles were not available for review.

The American College of Obstetrics & Gynecology[4] notes the following about naloxone and opioid withdrawal in pregnant women: "Although induced withdrawal may possibly contribute to fetal stress, naloxone should be used in pregnant women in the case of maternal overdose in order to save the woman's life."

UpToDate[5] notes the following regarding antenatal fetal monitoring following opioid overdose and naloxone administration: "The optimal method of fetal assessment during initial patient stabilization and initiation of pharmacotherapy ("induction") is unknown; no data are available to support any protocol."

Reviewer's comment: Although induced opioid withdrawal may contribute to fetal stress, naloxone should be used in pregnant women with known or suspected opioid overdose in order to save the woman's life. Additionally, the optimal method for fetal assessment during patient stabilization is unknown, and there are no data to support an approved protocol for fetal assessment and monitoring for opioid withdrawal. (b) (4)

The applicant did not perform a review of literature. Since DPMH was consulted late in the review cycle, an IR was not sent to the applicant, and DPMH did not conduct a thorough review but a brief review of the literature. The reader is referred to the Discussion and Conclusions section at the end of this review for DPMH's opinion of the data and recommendations.

LACTATION

Nonclinical Experience

No animal lactation studies have been performed.

Pharmacovigilance Database

There are no reports of lactation in the clinical studies.

[4] Committee on Obstetric Practice. Opioid Use and Opioid Use Disorder in Pregnancy. ACOG Number 711. August 2017.

[5] UpToDate. https://www.uptodate.com/contents/search. Overview of management of opioid use disorder during pregnancy. Accessed 10/23/2020.

Reference ID: 4691494

DPMH Review of Literature

DPMH conducted a search in PubMed using the search terms "naloxone" AND "lactation/breastfeeding" and did not identify any articles.

LactMed[6] notes the following:

> "No information is available on the excretion of naloxone into breastmilk. Because it is not orally bioavailable, it is unlikely to affect the breastfed infant. However, if naloxone is required by the mother for an opiate overdose, she should withhold nursing until the opiate is out of her system…Naloxone does not affect suckling-induced secretion of oxytocin or prolactin in postpartum women."

Dr. Hale, a lactation expert, notes the following *Medications and Mothers' Milk*[7] :

> "Naloxone is poorly absorbed orally and plasma levels in adults are undetectable (<0.05 ng/mL) two hours after oral doses. Following intravenous use (0.4 mg), plasma naloxone levels averaged <0.084 µg/mL. Side effects are minimal except in narcotic-addicted patients. Its use in breastfeeding mothers would be unlikely to cause problems as its milk levels would likely be low and its oral absorption is minimal to nil. When administering this medication to a breastfeeding woman for a narcotic overdose, breastfeeding may need to be withheld for 12-24 hours due to the amount of narcotic in milk, and potential risk of adverse effects (respiratory depression, sedation)."

Micromedex[8] notes the following:

> "Infant risk cannot be ruled out… there is inadequate information to determine any possible risk associated with naloxone use in the breastfed infant. Exercise caution when considering the use of naloxone and the potential for adverse effects on the breastfed infant or from the mother's underlying clinical diagnosis or condition."

Reviewer's comment: The applicant did not perform a review of literature. Since DPMH was consulted late in the review cycle, an IR was not sent to the applicant, and DPMH conducted their own literature review. The reader is referred to the Discussion and Conclusions section at the end of this review for DPMH's opinion of the data and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Male rats were treated with 2 or 10 mg/kg naloxone for 60 days prior to mating. Female rats treated for 14-days prior to mating and throughout gestation with doses of naloxone (up to 19.5-times a maximum human dose of 5 mg/day based on body surface area comparison). There were no adverse effects on fertility.

The reader is referred to the the Pharmacology/Toxicology review by Carlic Huynh, Ph.D., for further details.

Review of Pharmacovigilance Database

The applicant did not report any cases of infertility in clinical trials conducted for naloxone.

[6] LactMed: https://www.ncbi.nlm.nih.gov/books/NBK501681/. Accessed 10/22/2020
[7] HalesMeds.com. Accessed 10/22/2020
[8] https://www.micromedexsolutions.com/micromedex2/librarian/ssl/true. Accessed 10/22/2020

Reference ID: 4691494

DPMH review of literature:
DPMH conducted a search of published literature using the search terms "naloxone" AND "fertility/infertility/reproduction/sperm" and did not identify any relevant publications.

Reviewer's comment: The applicant did not perform a review of literature. Since DPMH was consulted late in the review cycle, an IR was not sent to the applicant, and DPMH did not conduct a thorough review but a brief review of the literature. The reader is referred to the Discussion and Conclusions section at the end of this review for DPMH's opinion of the data and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy
Animal reproduction studies have not identified any adverse developmental outcomes with naloxone use during pregnancy. Additionally, naloxone has been used for decades and available data from retrospective cohort studies on naloxone use in pregnant women have not identified a drug-associated risk of major birth defects or miscarriage. Currently approved naloxone labeling notes that naloxone crosses the placenta, and there is the potential for neonatal and maternal opioid withdrawal. Although induced opioid withdrawal may contribute to fetal stress, naloxone should be used in pregnant women with known or suspected opioid overdose in order to save the woman's life. Additionally, the optimal method for fetal assessment during patient stabilization is unknown and there are no data to support an approved protocol for fetal assessment and monitoring for opioid withdrawal. Therefore, information about naloxone precipitating opioid withdrawal in the fetus will not be included in naloxone hydrochloride injection labeling.

Since opioid overdose is a life-threatening situation, naloxone should not be withheld in pregnant women. Labeling will now include this updated information in 8.1 Risk Summary and Clinical Considerations.

Lactation
There is no information regarding the use of naloxone in lactating animals or humans. Based on the drug's characteristics (small molecular size, short-half, poor oral bioavailability), it is unlikely that naloxone will accumulate in human milk or adversely affect the breastfed infant. Additionally, since the indication is for emergent treatment of opioid withdrawal, DPMH recommends that the standard risk/benefit statement not be included in subsection 8.2 of naloxone labeling based on a PLLR Policy Working Group decision made on May 7, 2019.

Females and Males of Reproductive Potential
There does not appear to be any new information regarding naloxone and fertility since 2016; however, a brief review was done due to the late DPMH consultation. Animal fertility data for naloxone do not demonstrate effects on animal fertility. Subsection 8.3 Females and Males of Reproductive Potential will be omitted in the naloxone labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH recommendations are below, and DPMH refers to the final NDA action for final labeling.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7/6/2020

TO: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 212854

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the site in October 2018, which falls within the surveillance interval. The inspection was conducted under the following submissions: NON-RESPONSIVE NON-RESPONSIVE

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observations NON-RESPONSIVE

NON-RESPONSIVE

After receiving a written response from the sponsor, OSIS determined that the site's corrective and preventative actions were acceptable. Because, this observation had minimal impact on subject safety and data reliability and the site's overall study conduct was adequate, OSIS recommended that all study data were reliable to support a regulatory decision (OSIS Final EIR Review - October 2018).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Worldwide Clinical Trials (WCT) Early Phase Services, LLC.	2455 Northeast Loop 410, Suite 150, San Antonio, TX

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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6/23/2020

TO: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 212854

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: NON-RESPONSIVE.

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale provided above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

FOLAREMI ADEYEMO
06/23/2020 11:36:00 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	October 21, 2019
To:	Sharon Hertz, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	TRADENAME (naloxone hydrochloride injection)
Dosage Form and Route:	
Application Type/Number:	NDA 212854
Applicant:	Target Health Inc.

Reference ID: 4509413

1 INTRODUCTION

On December 31, 2018, Target Health Inc. submitted for the Agency's review a New Drug Application (NDA) 212854 for TRADENAME (naloxone hydrochloride injection). The proposed indication for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients.. On January 11, 2019, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU)] for TRADENAME (naloxone hydrochloride injection).

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for TRADENAME (naloxone hydrochloride injection).

2 CONCLUSIONS

Due to outstanding deficiencies, DAAAP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 15, 2019

TO: Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Office of New Drugs

Mary T. Thanh Hai, M.D.
Director (Acting)
Division of Anesthesia, Analgesia, & Addiction Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Routine inspection of Covance Clinical Research Unit, Inc., Dallas, TX

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of studies NON-RESPONSIVE and APC 6000-01 (NDA 212854) conducted at Covance Clinical Research Unit (Covance), Inc., Dallas, TX.

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

1.1. Recommendation

An objectionable condition was observed during this inspection for study NON-RESPONSIVE However, the inspectional finding did not impact the reliability of the clinical data from the study. Thus, the clinical data from studies NON-RESPONSIVE

NON-RESPONSIVE and APC 6000-01 (NDA 212854) and other studies of similar design are reliable to support a regulatory decision.

2 Inspected Studies:

NON-RESPONSIVE

NDA 212854

Study Number: APC 6000-01
Study Title: "An Open-label, Randomized, Single-dose, 2-period, 2-treatment Crossover Bioavailability Study Comparing 5 mg/0.5 mL of Intramuscular Naloxone Hydrochloride to 2 mg/0.4 mL Intramuscular Naloxone Hydrochloride Autoinjector (EVZIO®, Kaleo, Inc.) in Healthy Subjects"
Dates of conduct: 04/16/2018 – 04/28/2018

Clinical site: Covance Clinical Research Unit, Inc.
1341 W Mockingbird Ln Ste 200E
Dallas, TX 75247

ORA investigators Andrace Deyampert and Travis M Beard inspected Covance, Dallas, TX from June 03-07, 2019.

The inspection included a thorough examination of study records, subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

3 Inspectional Findings
At the conclusion of the inspection, investigators Deyampert and Beard observed an objectionable condition and Form FDA 483 was issued to the clinical site. Investigators also discussed two items with the site. The Form FDA 483 observation (**Attachment 1**), the firm's response dated 06/21/2019 (**Attachment 2**), discussion items, and my evaluation are presented below.

Reference ID: 4478126

3.1 FDA 483 Observation

(b) (4)

OSIS Evaluation: Covance's corrective and preventative actions are acceptable. Based on the study protocol of NON-RESPONSIVE

NON-RESPONSIVE

Therefore, this observation has minimal impact to the data reliability.

3.2 Discussion Items

(b) (4)

OSIS Evaluation: This item does not impact the clinical data reliability or subject safety. The collected exhibits showed that the covered area in source records by study sticker did not affect clinical data evaluation or reporting (**Attachment 3**). For subject (b) (6) enrolled in study APC 6000-01, the site did not

Reference ID: 4478126

report any AE event. Therefore, the missing respiration results for subject (b) (6) are not likely to impact subject safety.

(b) (4)

OSIS Evaluation: This item does not impact the clinical data reliability, because the site reported protocol deviations when sample collections occurred outside the protocol specified timeframe.

4. Conclusion:

An objectionable condition was observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable condition did not impact the reliability of the data from the audited studies. In addition, the overall performance of the site was adequate and is unlikely to impact the integrity of the data from other studies of similar design.

I conclude the clinical data from studies NON-RESPONSIVE NON-RESPONSIVE and APC 6000-01 (NDA 212854) are reliable. In addition, studies of similar design conducted between the previous inspection (b) (4) and the end of the current surveillance interval should also be considered reliable without an inspection.

Xiaohan Cai, Ph.D.
Senior Staff Fellow

Final Classification:

VAI– Covance Clinical Research Unit, Inc.
Dallas, TX
FEI#: 3007024261

cc:
OTS/OSIS/Kassim/Dasgupta/Mitchell/Fenty-Stewart/
OTS/OSIS/DNDBE/Bonapace/Au/Ayala/Biswas/
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Cai

Reference ID: 4478126

ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: XHC 08/14/2019; 08/15/19
Edit: JC 08/15/2019

ECMS: Cabinets/CDER/OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Covance Clinical Research Unit, Inc., Dallas, TX, USA

OSIS File #: 8382 (NDA 212854)and NON-RESPONSIVE

FACTS: 11911178

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Reference ID: 4478126

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/s/

XIAOHAN CAI
08/15/2019 04:03:00 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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Addendum to Review

Date:	August 8, 2019
From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Hari Cheryl Sachs, MD, Medical Team Leader DPMH
NDA Number:	212,854
Sponsor:	Adamis Pharmaceuticals
Drug:	Naloxone hydrochloride (HCl)
Indication:	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients.
Dosage Form and Route of Administration:	5 mg/0.5 mL, injection in pre-filled syringe
Proposed Dose Regimen:	5 mg (fixed dose), with repeat administration every 2 to 3 minutes
Division Consult Request:	The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requests DPMH assistance with the labeling review for this 505(b)(2) application.

Addendum to Consult Review of August 7, 2019

The applicant submitted a 505(b)(2) application for naloxone HCl for the indication of emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients.

(b) (4)

After submission of the application, the sponsor decided to perform the comparison study between the candidate product and 2 mg/2mL Intramuscular Naloxone Hydrochloride Injection (1mg/1mL, International Medical Systems) (b) (4) No new preclinical studies or clinical studies (adult or pediatric) are planned.

<u>Reviewer comment</u>: The acceptability of the results of the bioavailability study comparing the candidate product to Narcan will be reviewed by DAAAP and other FDA disciplines.

If after review, this bioavailability study is deemed acceptable, DPMH labeling recommendations remain unchanged.

Reference ID: 4474577

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ETHAN D HAUSMAN
08/08/2019 01:27:07 PM

HARI C SACHS
08/09/2019 09:12:49 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date:	August 7, 2019
From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Hari Cheryl Sachs, MD, Medical Team Leader DPMH
NDA Number:	212,854
Sponsor:	Adamis Pharmaceuticals
Drug:	Naloxone hydrochloride (HCl)
Indication:	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients.
Dosage Form and Route of Administration:	5 mg/0.5 mL, injection in pre-filled syringe
Proposed Dose Regimen:	5 mg (fixed dose), with repeat administration every 2 to 3 minutes
Division Consult Request:	The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requests DPMH assistance with the labeling review for this 505(b)(2) application.

Background

The applicant submitted a 505(b)(2) application for naloxone HCl for the indication of emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients. (b) (4) The application triggers PREA by proposing a new dosing regimen for the active drug (naloxone).

Dosing Regimens:

(b) (4)

- Narcan (injection; 0.02, 0.4, and 1 mg/mL per vial); Initial dose is 0.4 mg to 2 mg of IV, IM, or SC. May be repeated every 2 to 3 minutes as needed until 10 mg of Narcan have been administered, after which the diagnosis of opioid-related toxicity should be questioned.
- Candidate drug (injection; 5 mg/0.5 mL per prefilled syringe); fixed dose, with repeat administrations every 2 to 3 minutes. When additional doses are needed, labeling does not include a maximum recommended dose.

  Reviewer comment: At the internal meeting of July 15, 2019, the review team (DAAAP, Clinical Pharmacology, and DPMH) reached consensus that the proposed dose for the candidate product is safe for pediatric patients of all ages including neonates based on the following:

  - *There are no preclinical data suggesting safety issues at the proposed dose.*
  - (b) (4)
  - *Labeling for the few naloxone products which include a maximum dose (specifically, NDA 16,636) suggests that the recommendation to suspend administration of repeat doses after 10 minutes is intended to trigger clinical reassessment for patients with lack of response rather than for dose limiting toxicities*

The application was submitted without an agreed initial pediatric study plan (iPSP) or pediatric assessment. In lieu of rendering a refuse-to-file decision, FDA's 74-day letter (March 13, 2019) to the sponsor requested that the sponsor submit a pediatric assessment.

Reference ID: 4473768

The pediatric plan was received May 20, 2019 and is referenced to both the IND (136,148) and the NDA (212,854). (b) (4) [redacted] No new preclinical studies or clinical studies (adult or pediatric) are planned.

Reviewer comment: (b) (4) [redacted] *and is under review by DAAAP and other FDA disciplines.*

Presentation: The candidate product is being developed for emergency treatment of suspected or witnessed acute opioid overdose and will be marketed as a single unit dose presentation with a 25-gauge needle with a length of 5/8 inches.

Reviewer comment: The original naloxone labeling (NDA 16, 636) contains instructions for preparation of IV infusions. Given the presentation and labeling instructions, the candidate product will likely not be used off-label for preparation of IV infusions.

Reviewer comment: Because the needle length and gauge are similar to other marketed naloxone products, the presentation does not appear to pose new safety concerns. DPMH [formerly, Pediatric Maternal Health Staff (PMHS)] reviewed the length and gauge of such needles for other naloxone applications and determined that the needle (gauge and exposed needle length) is safe for use in children of all ages including neonates.[1]

This review is based on sponsor's draft labeling available on March 12, 2019. This review will focus on sections 1 (Indication), 2 (Dosing and Administration), and 8.4 (Pediatric Use). The text of sections 5 (Warnings and Precautions), 6 (Adverse Reactions) have been reviewed and are substantially similar to the reference product; therefore, additional review of these sections is deferred to DAAAP. There is no 14.1 (Clinical Studies) for naloxone products. Because the product will be approved for children of all ages including neonates, pediatric information is appropriately distributed throughout labeling.

DPMH has reviewed an agrees with the proposed language in the sections noted above and has no recommended revisions (see below).

1. Indications and Usage

PRODUCT™ is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients.

PRODUCT™ is intended for immediate administration as emergency therapy in settings where opioids may be present.

PRODUCT™ is not a substitute for emergency medical care.

[1] NDA 205,787. E Wynn. PMHS review. March 20, 2014.

Reference ID: 4473768

Reviewer comment: The indication statement is the same as several recently approved naloxone products for IM and nasal administration and is acceptable.[2,3]

2. Dosing and Administration

Initial Dosing

Administer the initial dose of PRODUCT™ to adult or pediatric patients intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary, and seek emergency medical assistance. Administer PRODUCT™ as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death.

Repeat Dosing

The requirement for repeat doses of PRODUCT™ depends upon the amount, type, and route of administration of the opioid being antagonized.

If the desired response is not obtained after 2 or 3 minutes, an additional dose of PRODUCT™ may be administered. If there is still no response and additional doses are available, additional doses of PRODUCT™ may be administered every 2 to 3 minutes until emergency medical assistance arrives. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

If the patient responds to PRODUCT™ and relapses back into respiratory depression before emergency assistance arrives, (b) (4)

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and may require higher doses of naloxone hydrochloride or repeated administration of PRODUCT™.

Dosing in Adults and Pediatric Patients (b) (4)

Instruct patients or their caregivers to administer PRODUCT™ according to the Instructions for Use, intramuscularly or subcutaneously.

Dosing in Pediatric Patients under Age One Year

In pediatric patients under the age of one year, the caregiver should pinch the thigh muscle while administering PRODUCT™. Carefully observe the administration site for signs of infection following injection and resolution of the opioid emergency.

(b) (4)

Reviewer comment: The above language is the same as recently approved naloxone products for injection and is acceptable.[4]

[2] (b) (4)

[3] NDA 208,411, Naloxone hydrochloride (nasa spray). Labeling. January 24, 2017.

[4] (b) (4)

Reference ID: 4473768

8.4 Pediatric Use

The safety and effectiveness of PRODUCT™ (for intramuscular and subcutaneous use) have been established in pediatric patients of all ages for the emergency treatment of known or suspected opioid overdose. Use of naloxone hydrochloride in all pediatric patients is supported by adult bioequivalence studies coupled with evidence from the safe and effective use of another naloxone hydrochloride injectable product. No pediatric studies were conducted for PRODUCT™.

Absorption of naloxone hydrochloride following subcutaneous or intramuscular administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds appropriately to naloxone hydrochloride injection, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.

In opioid-dependent pediatric patients, (including neonates), administration of naloxone hydrochloride may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. Unlike acute opioid withdrawal in adults, acute opioid withdrawal in neonates manifesting as seizures may be life-threatening if not recognized and properly treated. Other signs and symptoms in neonates may include excessive crying and hyperactive reflexes. In these settings where it may be preferable to avoid the abrupt precipitation of acute opioid withdrawal symptoms, consider use of an alternative, naloxone hydrochloride product that can be dosed according to weight and titrated to effect. [see Warnings and Precautions (5.3)].

In pediatric patients under the age of one year, the caregiver should pinch the thigh muscle while administering PRODUCT™. Carefully observe the administration site for evidence of residual needle parts, signs of infection, or both. [see Dosing Information (2.2)].

Reviewer comment: The above language is the same as several recently approved naloxone products,[5] accurately reflects the basis of pediatric approval, and is acceptable.

Conclusion

The above recommendations comments were shared with DAAAP on August 7, 2019**.** The reader is directed to the final negotiated labeling which may include changes to the above language.

[5] (b) (4)

Reference ID: 4473768

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/s/

ETHAN D HAUSMAN
08/07/2019 12:43:58 PM

HARI C SACHS
08/07/2019 12:53:09 PM
I agree with these labeling recommendations.

USE-RELATED RISK ANALYSIS, COMPARATIVE ANALYSES, AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 24, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 212854
Product Type:	Combination Product
Drug Constituent Name and Strength	Zimhi (naloxone HCl) 5 mg/0.5 mL
Device Constituent:	Pre-filled Syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Adamis Pharmaceuticals Corporation (Adamis)
Submission Date:	12/31/18 and 01/29/2019
OSE RCM #:	2019-8; 2019-15
DMEPA Human Factors Evaluator:	Jason Flint, MBA, PMP
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader (Acting):	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

Reference ID: 4467944

1. REASON FOR REVIEW

Adamis submitted a use-related risk analysis (URRA) and comparative analysis to support their determination that they do not need to submit the results of a HF validation study for their proposed product, Zimhi (naloxone HCl) pre-filled syringe for intramuscular or subcutaneous injection under NDA 212854. Zimhi is intended to treat opioid overdose, and is a combination product with a proposed pre-filled syringe device constituent part.

The review evaluates the submitted URRA and comparative analyses. This review also evaluates the proposed labels and labeling to identify areas of vulnerability that may lead to medication errors. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested this review as part of their evaluation of the 505(b)(2) NDA submission for Zimhi.

We conducted two previous human factors (HF) reviews for the Symjepi comparator[1], but were not engaged in the product development for the Zimhi product under the IND.

1.1 PRODUCT DESCRIPTION

Adamis proposes the Symjepi (epinephrine) pre-filled syringe as a comparator for their proposed Zimhi (naloxone HCl) product. See Appendix A for more details.

(b) (4)

[redacted]

[1] Owens, Lissa. Human Factors Review for Symjepi (Epinephrine) NDA 207534. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017-Apr-10. RCM No.: 2016-142, 2016-875.

Owens, Lissa. Human Factors Review for Symjepi (Epinephrine) NDA 207534. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016-Mar-23. RCM No.: 2016-875.

Reference ID: 4467944

Symjepi Comparator (left) and Proposed Device

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

DMEPA reviewed two HF validation study reports[2,3], and conducted a label and labeling review[4] for the Symjepi comparator product under NDA 207534. Symjepi was approved on 06/15/2017 for the emergency treatment of severe allergic reaction (Type 1) including anaphylaxis.

[2] Owens, Lissa. Human Factors Review for Symjepi (Epinephrine) NDA 207534. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017-Apr-10. RCM No.: 2016-142, 2016-875.

[3] Owens, Lissa. Human Factors Review for Symjepi (Epinephrine) NDA 207534. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016-Mar-23. RCM No.: 2016-875.

[4] Owens, Lissa. Label and Labeling Review for Symjepi (Epinephrine) NDA 207534/S-003. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018-Feb-28. RCM No.: 2018-209.

Reference ID: 4467944

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Use-related risk analysis and comparative analyses	C
Information Requests Issued During the Review	D
CDRH Human Factors Consult Review	N/A
Product Sample, Label and Labeling, Packaging	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide our evaluation of the use-related risk analysis and comparative analyses.

3.1 USE RELATED RISK ANALYSIS

We reviewed the URRA for Zimhi (naloxone HCl) and agree that the tasks evaluated are comprehensive and appropriate. We also reviewed the URRA to ensure that all potential risks, to include known use issues with currently marketed products have been considered and mitigated adequately. We did not identify any new or unique risks.

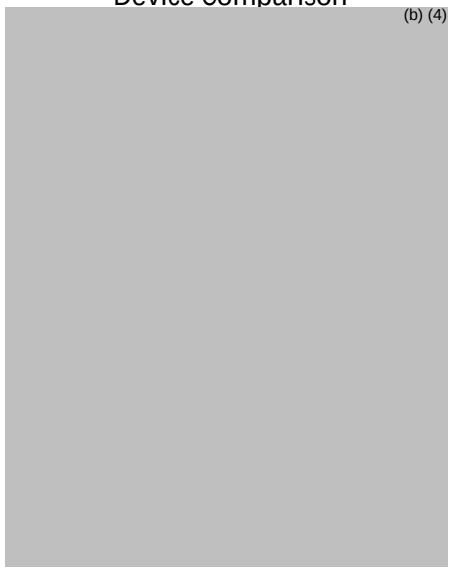
3.2 COMPARATIVE ANALYSIS

Table 2 describes Adamis's comparative analyses of their proposed product as compared to the comparator product. We reviewed the comparative task analysis, physical comparison, and labeling (IFU) comparison analysis.

Additionally, we reviewed the intended use, use environments, user tasks, and product presentations. Noted differences are discussed in table 2.

Reference ID: 4467944

Table 2. Comparative Analyses for Zimhi (naloxone HCl) and Symjepi (epinephrine)

	Differences Identified Between: Symjepi (Left) Zimhi (Right)	Applicant's Assessment of the Differences	DMEPA's Assessment of the Differences
Physical comparison of the delivery device constituent part	Device Comparison (b) (4)  The device constituent parts differ in color, (b) (4)	The Symjepi and Naloxone HCL devices have the same shape, size, instruction labels, use instructions and case. The Naloxone HCL device was designed so the user will have the same experience in administering the Naloxone as they do in administering the Symjepi products.	The delivery device constituent parts differ in color, and the (b) (4) We find the color difference of the proposed delivery device constituent part acceptable from a medication error perspective, because this difference does not impact a critical task. (b) (4)

	Differences Identified Between: Symjepi (Left) Zimhi (Right)	Applicant's Assessment of the Differences	DMEPA's Assessment of the Differences
	Case Comparison (b) (4)  The device constituent part cases differ in color, (b) (4)	The Naloxone HCL device was designed to fit within the same outer housing as Symjepi, have the same profile as Symjepi, and the same length. Both devices' housing profile is approximately 75mm tall x 29mm wide.	We compared the Zimhi (naloxone HCl) case to the Symjepi (epinephrine) comparator and note that the case is different only in color. We find the color difference for the proposed delivery device constituent part case acceptable from a medication error perspective because this difference does not impact a critical task.

	Differences Identified Between: Symjepi (Left) Zimhi (Right)	Applicant's Assessment of the Differences	DMEPA's Assessment of the Differences
	(b) (4)		We note that the proposed product has internal component design changes. However, we view these changes as minor differences because they do not impact critical tasks for this product. In addition, our review confirmed no additional physical differences. Based on the available information, we do not have any recommendations.

	Differences Identified Between: Symjepi (Left) Zimhi (Right)	Applicant's Assessment of the Differences	DMEPA's Assessment of the Differences
	(b) (4)		
			We note that the proposed product (b) (4) However, the (b) (4) do not appear to change the device's functionality, and may not affect any critical tasks. We find this aspect of the proposed delivery device constituent part acceptable from a medication error perspective.
Comparative Task Analysis	Intended users for both products are the same and they both are trained and untrained patients and caregivers.		We disagree that the intended users are the same for both products. While Symjepi is likely to be used by both patients and caregivers, Zimhi is likely to be used by the caregiver only given

	Differences Identified Between: Symjepi (Left) Zimhi (Right)	Applicant's Assessment of the Differences	DMEPA's Assessment of the Differences
			the proposed indication. Our evaluation indicates that since patients are not part of the intended user population, the sponsor has removed language/references to self-administration, which is reasonable. Therefore, we find that a results of HF validation study do not need to be submitted for our review as part of the product marketing application.
Labeling Comparison	1.Case [redacted] (b) (4)	The front case labels are the same in size [redacted] (b) (4) The Naloxone product name has not yet been assigned. [redacted] (b) (4)	We note a difference between the front case label for Zimhi and the comparator – [redacted] (b) (4) . We provide a recommendation to the applicant in section 4.2.

	Differences Identified Between: Symjepi (Left) Zimhi (Right)	Applicant's Assessment of the Differences	DMEPA's Assessment of the Differences
	(b) (4)		
	2.Case Back (b) (4)	The back case labels are the same in size and text except for the product names. The Naloxone product name has not yet been assigned. Use Instructions are the same.	We note differences in the back case label for Zimhi compared to Symjepi – some text on the Zimhi label is not in bold type, such as *DO NOT* and *Instructions for Use.* Since the Symjepi back case label has been validated through an HF validation study, the Zimhi label should have bold text for the words "DO NOT" and "Instructions for Use". We provide a recommendation to the applicant in section 4.2.

	Differences Identified Between: Symjepi (Left) Zimhi (Right)		Applicant's Assessment of the Differences	DMEPA's Assessment of the Differences
	3.Syringe Front label	3.Syringe Front label	(b) (4)	(b) (4) Thus, we provide a recommendation in Table 4.
	(b) (4			

	Differences Identified Between: Symjepi (Left) Zimhi (Right)	Applicant's Assessment of the Differences	DMEPA's Assessment of the Differences
	4.Syringe Back Label 4.Syringe Back Label (b) (4)	The syringe back labels are of the same size and shape. (b) (4) Product names and distributor are different. Text color is different. Use Instructions are the same.	We note differences in text color and distributor between the Zimhi and Symjepi syringe back labels. (b) (4) text color provides good contrast, therefore we find that, based on our heuristic review, these differences are not likely to contribute to medication error.
IFU Comparison	(b) (4)	Adamis did not address this change in their comparative analysis.	The statement in the Zimhi IFU is different than the Symjepi IFU, but is consistent with the different indications (for example, Symjepi is indicated for allergic emergencies, and Zimhi is indicated for opioid overdose). Therefore, we do not have additional concerns from a medication error perspective.

	Differences Identified Between: Symjepi (Left) Zimhi (Right)		Applicant's Assessment of the Differences	DMEPA's Assessment of the Differences
	(b) (4)		Adamis did not address this change in their comparative analysis.	(b) (4) Thus, we provide a recommendation in Table 4.
	The Symjepi IFU contains the statement "The pre-filled syringe cannot be reused."	(b) (4)		
	The Symjepi IFU contains the statement "Use second syringe if necessary. You may need a second Symjepi syringe if symptoms continue or recur."	The IFU submitted under 1.14.1.3 "Draft Labeling Text" contains the statement (b) (4)	Adamis did not address this change in their comparative analysis.	We find that the additional paragraph is a necessary component of the IFU, because it offers additional information about how often the medication can be delivered, and to seek medical attention for the patient.

	Differences Identified Between: Symjepi (Left) Zimhi (Right)		Applicant's Assessment of the Differences	DMEPA's Assessment of the Differences
		(b) (4) and has an additional paragraph: *If symptoms return after an injection with PRODUCT™, an additional injection using another PRODUCT™ prefilled syringe may be needed. Give additional injections using a new PRODUCT™ prefilled syringe every 2 to 3 minutes and continue to closely watch the person until emergency help is received. PRODUCT™ does not take the place of emergency medical care.*		This language is similar to other naloxone products for emergency use in non-healthcare settings. We have no additional concerns from a medication error perspective.

3.3 LABELS AND LABELING

Our evaluation of the proposed labels, labeling and packaging identified several areas of concern which are included in Tables 3 and 4. Tables 3 and 4 also include our recommendations to minimize the risk for medication errors.

3.4 INSTRUCTIONS FOR USE

We note that the prescribing information (PI) contains the statement, "In pediatric patients under the age of one, the caregiver should pinch the thigh muscle while administering the dose."; however, this statement is not included in the instructions for use (IFU). We contacted the clinical review team to determine if there are clinical concerns if a user fails to pinch the thigh before giving the injection to a patient under the age of one. The clinical reviewer's main concerns are the potential to hit the bone with the needle, potentially causing the needle to bend and break. A broken needle could result in a failed injection, or a foreign body in the leg. However, we note that this risk is similar to other injectable products that have been approved for patients less than 1 year of age. We determined that adding this statement to the IFU may be a sufficient risk mitigation strategy. Thus, we make a recommendation in section 4.2 to address our concern.

4. CONCLUSION AND RECOMMENDATIONS

Our review of the URRA and the comparative analyses show that there are no differences that impact critical tasks. Thus, we agree with Applicant's justification for not submitting the results of a human factors validation study.

Our evaluation of the proposed labels, labeling and packaging, identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Table 3 for the Division and Table 4 for Adamis. We ask that the Division convey Table 4 in its entirety to Adamis so that our recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DAAAP

Table 3. Identified Issues and Recommendations for DAAAP

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			

Reference ID: 4467944

1.	The placeholder, "Product™" is used throughout the Prescribing Information for the proprietary name.	We reference our March 27, 2019 proprietary name review (OSE # 2018-28372523), concluding that the proprietary name, Zimhi, was found conditionally acceptable.	Revise the placeholder, "Product™", with the proprietary name, Zimhi, throughout the Prescribing Information.
2.	The dosage form is not consistently presented throughout the prescribing information (i.e. both "prefilled syringe" and "pre-filled syringe" are used).	To maintain consistency the dosage form should be the same throughout prescribing information.	Revise the dosage form term so that it is consistent throughout all labels and labeling (i.e. use either prefilled syringe or pre-filled syringe).
Full Prescribing Information			
1.	The Dosage Forms and Strengths section and the How Supplied section (b) (4) [redacted]	These important identifying characteristics of the drug product should be included in the Dosage Forms and Strengths section per 21 CFR 201.57(c)(4)(ii). Furthermore, this information should be included in the How Supplied section per 21 CFR 201.57(c)(17).	Include that the solution is clear in these sections. For example, in the Dosage Forms and Strengths section: "5 mg Injection: 5 mg/0.5 mL naloxone hydrochloride is a clear (b) (4) [redacted] In the How Supplied section: (b) (4) [redacted]
2.	In the How Supplied section, the NDC (National Drug Code) is denoted by a	Per 21 CFR 201.57(c)(17)(iii), the How supplied section should include "Appropriate	We have provided a recommendation in Table 3 below for the Applicant to

	placeholder (i.e. NDC xxxxxx).	information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number;".	include the NDC on the carton labeling once assigned.

4.2 RECOMMENDATIONS FOR ADAMIS PHARMACEUTICAL COMPANY

Based on our review of your use-related risk analysis (URRA), comparative analyses, and justification, we have determined that you do not need to submit the results of a human factors validation study to support your NDA. Please note that if you modify the product user interface, additional human factors considerations may apply.

Our evaluation of the proposed labels, labeling and packaging identified areas of vulnerability that may lead to medication errors. We provided recommendations in the table below.

Table 4. Identified Issues and Recommendations for Adamis (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issue			
1.	The placeholder "Product™" is used throughout the labels and labeling for the proprietary name. Furthermore, the trademark "TM" abbreviation is prominently displayed next to the placeholder.	We reference our March 28, 2019 letter informing you that the proprietary name, Zimhi, was found conditionally acceptable. Furthermore, a prominently displayed trademark abbreviation may be misinterpreted as being part of the proprietary name and lead to confusion.	Revise all labels and labeling that contain the placeholder, "Product™" with the proprietary name Zimhi. Also, revise the "TM" abbreviation to ensure that it does not compete in prominence with the proprietary or established name.
Syringe label			

1.	(b) (4) [redacted]		We recommend changing this image (b) (4) [redacted]
Syringe label, Case labeling and Inner Carton labeling and Outer Carton labeling			
1.	The route of administration has been omitted.	The route of administration is critical information that should be included on the Principal Display Panel (PDP).[5]	Add the route of administration, For intramuscular or subcutaneous injection, to the PDP of the syringe label, case labeling and carton labeling.
2.	The format of the expiration date has been omitted from the draft syringe label, case labeling, inner carton labeling, and outer carton labeling. We noted that the placebo product samples that were submitted have the expiration date denoted as MMM-YY (example JAN 01) for the syringe label, case	The use of confusing expiration date formats has led to misinterpretation and deteriorated drug medication errors. For example, JAN 01 may be interpreted as January 2001 or misinterpreted as January 1st.	As currently presented, the format for the expiration date that was included in the product samples may cause confusion. To minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the

[5] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

	label and inner carton labeling.		expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Case labeling and Inner Carton labeling and Outer Carton labeling			
1.	The case label includes the dosage form as "prefilled syringe" while all other labeling includes a hyphen in the dosage form (i.e. pre-filled syringe).	To maintain consistency the dosage form should be the same throughout all labels and labeling.	Revise the dosage form term so that it is consistent throughout all labels and labeling (i.e. use either prefilled syringe or pre-filled syringe).
2.	As currently presented, the NDC number is denoted by a placeholder.	During distribution, dispensing, and administration the NDC is often used to confirm a drug product.	Once assigned, please submit NDCs for all the case labeling and carton labeling. Please ensure that the package code portion (last 1-2 digits) is different and non-sequential between the case labeling, carton labeling and outer carton labeling.
Inner Carton labeling and Outer Carton labeling			

1.	The established name lacks prominence on the carton labeling.	Per 21 CFR 201.10(g)(2), the established name should be at least half the size of the proprietary name.	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
2.	The strength on the front Principal Display Panel (PDP), back panel, top panel and side panels is (b) (4)	This strength presentation is inconsistent with the strength presentation provided in the Prescribing Information, 5 mg/0.5 mL.	For consistency with the Prescribing information, revise the strength presentation on all panels to 5 mg/0.5 mL.
Inner Carton labeling			
1.	The carton labeling appears to contain a 2D data matrix barcode product identifier on the bottom panel but does not contain all of the recommended human readable product identifier information (and serial number).	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[6] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier	Review the draft guidance to determine if the product identifier requirements apply to your product's labeling. If so, we recommend that you add the human readable product identifier information for the serial number using the following format: SERIAL: [insert product's serial number]

[6] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

		requirements apply to your product's labeling.	
Case labeling			
1.	Some text on the back of the case labeling is not in bold type, such as "DO NOT" and "Instructions for Use" which is inconsistent with the case labeling for Symjepi.	Since the Symjepi back case labeling has been validated through an HF validation study, the Zimhi label elements should match when possible.	Revise the statements "Do not" and "Instructions for Use" on the back of the case labeling so that they are in bold type.
Instructions for Use			
1.	(b) (4)		We recommend changing this image (b) (4)
2.	Under the Section "Get Help (b) (4) the statement reads (b) (4)	(b) (4)	Revise the statement to, "Tell healthcare provider that you (b) (4) an injection of naloxone HCL." so that this instruction is directed towards caregivers.
3.	The back side of the IFU contains the statement: (b) (4)	While this appears to be a typographical error, it needs to be clarified.	If the intent of this statement is that (b) (4) please revise.

4.	The back side of the IFU contains the statement: (b) (4)	This statement does not seem relevant to opioid overdose patients because the patient would not be responsive regardless of age.	Remove this statement from the IFU.
5.	The back side of the IFU contains the statement: (b) (4)	These statements should be (b) (4)	Revise this statement to: "Tell the healthcare provider that you have received or administered an injection of naloxone HCL. Show the healthcare provider where the injection was administered. Give (b) (4) to the healthcare provider for inspection and proper disposal."
6.	The Prescribing Information contains instructions in the IFU to give additional injections every 2 to 3 minutes; (b) (4)	This important information should be included in the IFU that will be contained in the syringe case to alert users to the amount of time that they should wait before administering additional doses.	Add the statement "If symptoms return after an injection with "PRODUCT, an additional injection using another PRODUCT prefilled syringe may be needed. Give additional injections using a new PRODUCT prefilled syringe every 2 to 3 minutes and continue to closely watch the person until emergency help is received. Product does not take the place of emergency medical care." to the back side of the IFU that will be contained in the syringe case.

7.	The back side of the IFU contains the statement "Your Product Has an Expiration Date – Example (b) (4)	(b) (4) Furthermore, the use of confusing expiration date formats has led to misinterpretation and deteriorated drug medication errors.	Remove the statement "Example (b) (4) Furthermore, refer to the recommendation #2 for the syringe label, case labeling, inner carton labeling, and outer carton labeling for recommended expiration date formats to minimize confusion and reduce the risk for deteriorated drug medication errors.
8.	The PI contains the statement: "In pediatric patients under the age of one, the caregiver should pinch the thigh muscle while administering the dose." This statement has not been included in the IFU.	This important instruction should be included in the IFU to reduce the risk of administration errors while users are administering the product to patients under one years old.	Add this statement to Step 2 of the IFU.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Zimhi (naloxone HCl) received on 01/29/2019 from Adamis Pharmaceutical Corporation, and Symjepi (epinephrine).

Table 3. Relevant Product Information for Proprietary name and the Comparator Product

Product Name	Zimhi (naloxone HCl)	Symjepi (epinephrine)[7]
Initial Approval Date	N/A	11/15/2017
Therapeutic Drug Class or New Drug Class	Opioid antagonist	Non-selective alpha and beta-adrenergic receptor agonist
Active Ingredient	Naloxone HCl	Epinephrine
Indication	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.	Emergency treatment of allergic reactions (Type I)
Route of Administration	Injection	Injection
Dosage Form	Pre-filled syringe	Pre-filled syringe
Strength	5 mg/0.5 mL	0.3 mg/0.3 mL
Dose and Frequency	5 mg 2-3 minutes apart	0.3 mg can deliver up to 2 doses
How Supplied	Two pre-filled syringes in protective cases	Two pre-filled syringes in protective cases
Storage	Protect from light. Store at room temperature 59°F to 77°F (15°C to 25°C). Excursions permitted up to 104°F (40°C). Do not freeze.	Protect from light. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)
Container Closure/Device Constituent	Protective case containing two pre-filled syringes	Protective case containing two pre-filled syringes
Intended Users	Lay caregiver	Patients or lay caregiver

[7] Symjepi [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 MAY 08. Available from: https://www.accessdata fda.gov/drugsatfda_docs/label/2018/207534s003lbl.pdf

Intended Use Environment	Any environment	Any environment

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On 03/06/2019, we searched the L:drive and AIMS using the terms, '212854', 'Zimhi', and 'Symjepi' to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified three previous reviews[8,9,10] for the Symjepi comparator.

[8]Owens, Lissa. Human Factors Review for Symjepi (Epinephrine) NDA 207534. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017-Apr-10. RCM No.: 2016-142, 2016-875.

[9] Owens, Lissa. Human Factors Review for Symjepi (Epinephrine) NDA 207534. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016-Mar-23. RCM No.: 2016-875.

[1010] Owens, Lissa. Label and Labeling Review for Symjepi (Epinephrine) NDA 207534/S-003. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018-Feb-28. RCM No.: 2018-209.

Reference ID: 4467944

APPENDIX C. USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES

The use-related risk analysis and comparative analysis can be accessed in EDR via:

\\cdsesub1\evsprod\nda212854\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-opioid-over-dosage\5354-other-stud-rep\use-related-risk-analysis-hazard-analysis.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804d5d14&_afrRedirect=3432764095803936

APPENDIX E: CDRH HUMAN FACTORS CONSULT REVIEW

N/A

APPENDIX F. PRODUCT SAMPLE, LABELS AND LABELING, AND PACKAGING

F.1 Product Sample

F.2 List of Labels and Labeling Reviewed and Images

Using the principles of human factors and Failure Mode and Effects Analysis,[11] along with postmarket medication error data, we reviewed the following naloxone labels and labeling submitted by Adamis.

- Safety Label received on December 31, 2018
- Actuator Label received on December 31, 2018
- Syringe Label received on December 31, 2018
- Syringe Case Labeling received on December 31, 2018
- Inner Carton Labeling received on December 31, 2018
- Outer Carton Labeling received on December 31, 2018
- Instructions for Use received on December 31, 2018 and can be accessed in EDR via:
  - \\cdsesub1\evsprod\nda212854\0001\m1\us\draft-carton-container-labels.pdf
- Prescribing Information (Image not shown) received on April 2, 2019 and can be accessed in EDR via:
  - \\cdsesub1\evsprod\nda212854\0005\m1\us\draft-labeling-text.docx

[11] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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QUYNHNHU T NGUYEN
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/13/2019

TO: Division of Anesthesia Analgesia and Addiction Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 212854

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in August 2018, which falls within the surveillance interval. The inspection was conducted under the following submissions: NON-RESPONSIVE

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the outcome of the previous inspection and the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

ANGEL S JOHNSON
03/13/2019 03:43:19 PM